

**WARFARIN RESISTANCE GENOTYPE REFLEX PANEL**  
**#89458****PROFILE INFORMATION:**

Unit Code	Reporting Name	Available Separately	Always Performed
29564	Warfarin Resistance Genotype Interp	No	Yes
89608	Warfarin Resistance Mutation Scrn	No	Yes

**ADDITIONAL TESTS:**

Unit Code	Reporting Name	Available Separately	Always Performed
81769	Rapid DNA Extraction	No	Yes

**REFLEX TESTS:**

Unit Code	Reporting Name	Available Separately	Always Performed
29592	Warfarin Resistance Gene Sequence	No	No
89478	Warfarin Resistance Gene Sequencing	No	No

**TESTING ALGORITHM:**

- When this test is ordered, DNA extraction will always be performed at an additional charge.
- If #89608 "Warfarin Resistance Mutation Screen" is negative, #29592 "Warfarin Resistance Gene Sequence" and #89478 "Warfarin Resistance Gene Sequencing" will be performed at an additional charge.

**USEFUL FOR:**

- Assessing patients with inappropriately low INRs following warfarin therapy who may have mutations in *VKORC1* and require increased warfarin dosing to reach a therapeutic INR
- Assessing whether alternative anticoagulants may be better therapeutic options for management of patients with warfarin resistance

**METHODOLOGY:**

89608: Polymerase Chain Reaction (PCR) with Allele Specific Primer Extension (ASPE)

29592 and 89478: Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis

**REFERENCE VALUES:** An interpretive report will be provided.**SPECIMEN REQUIREMENTS:** Draw blood in a lavender-top (EDTA) tube(s), and send 3 mL of EDTA whole blood refrigerated in original VACUTAINER(S).**NOTE:** 1. Bone marrow and liver transplants will interfere with testing. For bone marrow transplant patients, buccal cells should be provided from the **recipient** to obtain an accurate genotype. For liver transplant patients, **donor** blood or buccal cells should be provided to obtain an accurate genotype for the recipient patient.

2. Transfusions will interfere with testing for up to 4 to 6 weeks. DNA obtained from white cells may not provide useful information for patients who received a recent transfusion of blood that was not leukocyte-reduced. Wait 4 to 6 weeks until transfused cells have left the patient's circulation before drawing the patient's blood specimen for genotype testing.

3. An "Informed Consent for DNA Testing" (Supply T576) is available. See Special Instructions (on-line test catalog) for a copy of the form.

**CAUTIONS:**

- Warfarin-resistance genotyping should only be performed on individuals who have a subtherapeutic INR (ie, < 2.0) at the appropriate warfarin dose based upon age, gender, and weight or body surface area. Warfarin-resistance genotyping should not be used for assessing individuals with an INR > 2.0 at the appropriate warfarin dose. Such individuals are not warfarin resistant, but may be warfarin sensitive and should have "Warfarin Sensitivity, "Genotype" testing (#89033) performed instead.
- This test does not detect genetic variants other than within the exons and near intron regions of *VKORC1*. Rare genetic variants in the primer-binding regions can affect test results. This method will not detect large rearrangement-type mutations or mutations that occur in the introns (except in the splicing regions) and regulatory regions of the gene.
- Absence of a mutation does not preclude the diagnosis of warfarin resistance unless a specific mutation has been previously identified in an affected family member.
- Sometimes a genetic alteration of unknown significance may be identified. In this case, testing of family members may be useful to determine pathogenicity of the alteration.
- Genotyping patients using DNA obtained from leukocytes may not provide useful information in patients who have had a bone marrow or liver transplant or a recent transfusion. To obtain an accurate genotype on a bone marrow transplant recipient, buccal cells should be provided. To obtain an accurate genotype for a patient who has received a donor liver, testing must be performed on donor cells. After transfusion, wait 4 to 6 weeks until transfused cells have left the circulation.
- Warfarin resistance may also be due to nongenetic factors, such as drug absorbance problems or excessive intake of vitamin K.

**LIST FEE:** #89458: \$272.40 plus \$150.00 for #81769 = \$442.40 (Total List Fee)  
#29592 and #89478: \$375.00 (if appropriate)

**CPT CODE:**

"Warfarin Resistance Genotype Interpretation"

83912

"Warfarin Resistance Mutation Screen"

83892/Enzymatic digestion

83900/Amplification, target, multiplex, first 2 nucleic acid sequences

83901/Amplification, target, multiplex, each additional nucleic acid sequence beyond 2

83914/x12 Mutation identification by enzymatic ligation or primer extension, single segment, each segment

"Rapid DNA Extraction"

83890

"Warfarin Resistance Gene Sequence"

83892/Enzymatic digestion (if appropriate)

83894/Separation by gel electrophoresis (if appropriate)

83900/Amplification, target, multiplex, first 2 nucleic acid sequences (if appropriate)

83901/Amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (if appropriate)

"Warfarin Resistance Gene Sequencing"

83909/x6 Mutation identification by sequencing, single segment, each segment (if appropriate)

**ANALYTIC TIME:** 7 days

**DAY(S) SET-UP:** Monday through Friday; Varies

QUESTIONS: Contact your Mayo Medical Laboratories' Regional Manager  
Shirley Pokorski, Mayo Medical Laboratories' Technologist Support  
Telephone: 800-533-1710



# TEST DEFINITION

5/4/2009

MML NAME/ORDER CODE CROSS-REFERENCE

CODE	NAME
89458	WARFARIN RESISTANCE GENOTYPE

MML TEST SETUP INFORMATION

ORDER CODE	EFF DATE	TC	TITLE	CHECKING NORMALS	PRINT NORMALS (# CODED)	PERFORM SITE *
89458 (PROFILE)			WARFARIN RESISTANCE GENOTYPE			
29564	2/26/2009		WARFARIN RESISTANCE GENOTYPE INTERP			MCR
			UNIT CODE ALWAYS MESSAGE - [ZIUO]			
			INVESTIGATIONAL USE ONLY			
			TRANSPORT TEMP : AMBIENT\REFRIG OK\FROZEN OK			
			29564	WARFARIN RESISTANCE GENOTYPE INTERP		
			-	-	-	-
			29565	WARFARIN RES GENOTYPE REVIEWED BY		
			POSSIBLE RESULT VALUES INCLUDE : DENNIS J. O'KANE, PH.D., JOHN L. BLACK, M.D., LINNEA M. BAUDHUIN, PH.D., LORALIE J. LANG.			
			-	-	-	-
89608	2/26/2009		WARFARIN RESISTANCE MUTATION SCRIN			MCR
			UNIT CODE ALWAYS MESSAGE - [ZIUO]			
			INVESTIGATIONAL USE ONLY			
			TRANSPORT TEMP : AMBIENT\REFRIG OK\FROZEN OK			
			29566	VKORC1 85G>T		
			-	-	-	-
			29567	VKORC1 121G>T		
			-	-	-	-
			29568	VKORC1 134T>C		
			-	-	-	-
			29569	VKORC1 172A>G		
			-	-	-	-
			29570	VKORC1 1331G>A		
			-	-	-	-
			29571	VKORC1 3487T>G		
			TEST CODE ALWAYS MESSAGE - [Z89458]			
			Z89458 A TWO-TIERED TESTING APPROACH IS USED TO IDENTIFY MUTATIONS WITHIN THE VKORC1 GENE. TIER 1 CONSISTS OF DIRECT MUTATION ANALYSIS FOR THE MOST FREQUENTLY REPORTED VKORC1 MUTATIONS 85G>T, 121G>T, 134T>C, 172A>G, 1331G>A, AND 3487T>G FOLLOWING POLYMERASE CHAIN REACTION			

(PCR) AMPLIFICATION AND ALLELE-SPECIFIC PRIMER EXTENSION.  
IF A MUTATION WAS IDENTIFIED IN TIER 1, THEN TESTING WAS  
STOPPED. TIER 2 CONSISTS OF FLUORESCENT DNA SEQUENCE  
ANALYSIS OF THE 3 EXONS AND EXON/INTRON BOUNDARIES OF  
THE VKORC1 GENE AND IS PERFORMED ONLY WHEN NO MUTATION  
IS IDENTIFIED IN TIER 1.

UNSUSPECTED GENETIC VARIANTS IN THE PRIMER BINDING  
REGIONS CAN AFFECT TESTING AND, ULTIMATELY, THE  
GENOTYPING CALLS MADE.

ABSENCE OF A VARIANT DOES NOT PRECLUDE THE DIAGNOSIS OF  
WARFARIN RESISTANCE UNLESS A SPECIFIC VARIANT HAS BEEN  
PREVIOUSLY IDENTIFIED IN AN AFFECTED FAMILY MEMBER.

SOMETIMES A GENETIC VARIATION OF UNDETERMINED  
SIGNIFICANCE MAY BE IDENTIFIED. IN THIS CASE, TESTING OF  
FAMILY MEMBERS MAY BE USEFUL TO DETERMINE ANY  
FUNCTIONALITY FOR THIS VARIATION.

WARFARIN RESISTANCE MAY ALSO BE DUE TO NON-GENETIC FACTORS,  
SUCH AS DRUG ABSORPTION PROBLEMS OR EXCESSIVE INTAKE OF  
VITAMIN K.

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MML MML TEST SETUP INFORMATION

\*PERFORMING SITE LEGEND

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MCR	MAYO CLINIC DPT OF LAB MED & PATHOLOGY	LAB DIRECTOR:	FRANKLIN R. COCKERILL, III, M.D.
	200 FIRST STREET SW		
	ROCHESTER, MN 55905		

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MML MESSAGES USED AS NORMALS

CODE TEXT

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TOTAL OF 0 NORMALS CODES

\*\*\* END OF REPORT \*\*\*



# TEST DEFINITION

2/11/2009

MML NAME/ORDER CODE CROSS-REFERENCE  
CODE NAME  
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81769 RAPID DNA EXTRACTION

MML		MML TEST SETUP INFORMATION				PERFORM	
ORDER CODE	EFF DATE	TC	TITLE	CHECKING NORMALS	PRINT NORMALS (# CODED)	SITE *	
81769	5/25/2007		RAPID DNA EXTRACTION			MCR	
			TRANSPORT TEMP : AMBIENT\FROZEN OK\REFRIG OK				
			28357 COMMENT				

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\*PERFORMING SITE LEGEND

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MCR	MAYO CLINIC DPT OF LAB MED & PATHOLOGY	LAB DIRECTOR:	FRANKLIN R. COCKERILL, III, M.D.
	200 FIRST STREET SW		
	ROCHESTER, MN 55905		

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MML MESSAGES USED AS NORMALS  
CODE TEXT  
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TOTAL OF 0 NORMALS CODES

\*\*\* END OF REPORT \*\*\*



# TEST DEFINITION

5/4/2009

MML NAME/ORDER CODE CROSS-REFERENCE

CODE NAME  
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29592 WARFARIN RESISTANCE GENE SEQUENCE

MML MML TEST SETUP INFORMATION

ORDER CODE	EFF DATE	TC	TITLE	CHECKING NORMALS	PRINT NORMALS (# CODED)	PERFORM SITE *
29592	3/19/2009		WARFARIN RESISTANCE GENE SEQUENCE			MCR
		29592	WARFARIN RESISTANCE GENE SEQUENCE			

\*PERFORMING SITE LEGEND

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MCR	MAYO CLINIC DPT OF LAB MED & PATHOLOGY	LAB DIRECTOR:	FRANKLIN R. COCKERILL, III, M.D.
	200 FIRST STREET SW		
	ROCHESTER, MN 55905		

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MML MESSAGES USED AS NORMALS

CODE TEXT  
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TOTAL OF 0 NORMALS CODES

\*\*\* END OF REPORT \*\*\*



# TEST DEFINITION

5/4/2009

MML NAME/ORDER CODE CROSS-REFERENCE

CODE NAME  
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89478 WARFARIN RESISTANCE SEQUENCING

MML MML TEST SETUP INFORMATION

ORDER CODE	EFF DATE	TC	TITLE	CHECKING NORMALS	PRINT NORMALS (# CODED)	PERFORM SITE *
89478	3/23/2009		WARFARIN RESISTANCE SEQUENCING			MCR

TRANSPORT TEMP :  
89478 WARFARIN RESISTANCE SEQUENCING  
POSSIBLE RESULT VALUES INCLUDE : TNP#XSEQ, PERFORMED, PERFORMED

\*PERFORMING SITE LEGEND

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MCR	MAYO CLINIC DPT OF LAB MED & PATHOLOGY	LAB DIRECTOR:	FRANKLIN R. COCKERILL, III, M.D.
	200 FIRST STREET SW		
	ROCHESTER, MN 55905		

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MML MESSAGES USED AS NORMALS  
CODE TEXT  
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TOTAL OF 0 NORMALS CODES

\*\*\* END OF REPORT \*\*\*



## LABORATORY SERVICE REPORT

1-800-533-1710

PATIENT NAME TESTING, WARFRES		PATIENT NUMBER		AGE 34	SEX M	ACCESSION # G9124108
ORDERING PHYSICIAN		CLIENT ORDER #				ACCOUNT # LIAISONS
COLLECTION 04/14/09 01:54 P	RECEIVED	REPORT PRINTED 05/04/09 01:14 P		SPECIMEN INFORMATION DATE OF BIRTH:		
DATE	TIME	DATE	TIME			
Test Client Attn: Mayo Liaisons 200 First Street SW Rochester, MN 55905 507-284-8202						

TEST REQUESTED	HI LO	REF RANGE	PERFORM SITE *
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**Warfarin Resistance Genotype Interp****Warfarin Resistance****MCR****Genotype Interp**

Although unlikely, this result does not rule out the possibility this patient may have a previously undescribed VKORC1 gene variant that cannot be identified by the method used in this assay. Warfarin resistance may be due to acquired factors or non-compliance, or deficiency in another gene involved in producing fully active coagulation factors.

**Warfarin Res Genotype**

Dennis J. O'Kane, Ph.D.

**MCR****Reviewed By****Warfarin Resistance Gene Sequence****Warfarin Resistance****MCR****Gene Sequence**

No mutation was detected in VKORC1.

**Rapid DNA Extraction****Comment**

Genomic DNA was extracted.

**MCR****Warfarin Resistance Sequencing****Warfarin Resistance**

Performed

**MCR****Sequencing****Warfarin Resistance Mutation Scrn**

VKORC1 85G&gt;T

G/G

**MCR**

VKORC1 121G&gt;T

G/G

**MCR**

VKORC1 134T&gt;C

T/T

**MCR**

VKORC1 172A&gt;G

A/A

**MCR**

VKORC1 1331G&gt;A

G/G

**MCR**

VKORC1 3487T&gt;G

T/T

**MCR**

\* Perform Site Legend on last page of report

PATIENT NAME TESTING, WARFRES	ORDER STATUS Final	COLLECTION DATE AND TIME 04/14/09 01:54 P
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## LABORATORY SERVICE REPORT

1-800-533-1710

PATIENT NAME TESTING, WARFRES		PATIENT NUMBER		AGE 34	SEX M	ACCESSION # G9124108
ORDERING PHYSICIAN		CLIENT ORDER #				ACCOUNT # LIAISONS
COLLECTION 04/14/09 01:54 P	RECEIVED	REPORT PRINTED 05/04/09 01:14 P		SPECIMEN INFORMATION DATE OF BIRTH:		
DATE	TIME	DATE	TIME			
Test Client Attn: Mayo Liaisons 200 First Street SW Rochester, MN 55905 507-284-8202						

TEST REQUESTED	HI LO	REF RANGE	PERFORM SITE *
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A two-tiered testing approach is used to identify mutations within the VKORC1 gene. Tier 1 consists of direct mutation analysis for the most frequently reported VKORC1 mutations 85G>T, 121G>T, 134T>C, 172A>G, 1331G>A, and 3487T>G following polymerase chain reaction (PCR) amplification and allele-specific primer extension. If a mutation was identified in tier 1, then testing was stopped. Tier 2 consists of fluorescent DNA sequence analysis of the 3 exons and exon/intron boundaries of the VKORC1 gene and is performed only when no mutation is identified in Tier 1.

Unsuspected genetic variants in the primer binding regions can affect testing and, ultimately, the genotyping calls made.

Absence of a variant does not preclude the diagnosis of warfarin resistance unless a specific variant has been previously identified in an affected family member.

Sometimes a genetic variation of undetermined significance may be identified. In this case, testing of family members may be useful to determine any functionality for this variation.

Warfarin resistance may also be due to non-genetic factors, such as drug absorption problems or excessive intake of vitamin K.

## \* PERFORMING SITE

MCR	Mayo Clinic Dpt of Lab Med & Pathology 200 First Street SW Rochester, MN 55905	Lab Director: Franklin R. Cockerill, III, M.D.
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PATIENT NAME TESTING, WARFRES	ORDER STATUS Final	COLLECTION DATE AND TIME 04/14/09 01:54 P
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Specimen receipt and report times are in CST/CDT

REPRINT

Page 2 of 2