Familial/Autosomal Dominant Hypercholesterolemia Diagnostic Algorithm

Clinical suspicion of autosomal dominant hypercholesterolemia (ADH); includes familial defective apolipoprotein B–100 and familial hypercholesterolemia.

Order ADHP / Familial Hypercholesterolemia/Autosomal Dominant Hypercholesterolemia Genetic Testing Reflex Panel

APOB genotype is performed for the common APOB pathogenic variants R3500Q and R3500W.

APOB pathogenic variant(s) detected
- Diagnostic of familial defective apolipoprotein B–100. Testing is stopped and an interpretive report is provided.
- Consider testing at-risk relatives for the familial pathogenic variants using tests:
  - KVAR1 / Known Variant Analysis-1 Variant
  - KVAR2 / Known Variant Analysis-2 Variants

No APOB pathogenic variants detected
- LDLR gene sequencing is automatically performed.
- LDLR pathogenic variant(s) detected by sequencing. Diagnostic of familial hypercholesterolemia. Testing is stopped and an interpretive report is provided.
- Consider testing at-risk relatives for the familial pathogenic variants using 1 of the following tests:
  - KVAR1 / Known Variant Analysis-1 Variant
  - KVAR2 / Known Variant Analysis-2 Variants
  - KVAR3 / Known Variant Analysis-3+ Variants

No LDLR pathogenic variants detected by sequencing.
- LDLR large deletion/duplication analysis is automatically performed.
- LDLR large deletion or duplication detected. Diagnostic of familial hypercholesterolemia. Interpretive report provided.
- Consider testing at-risk relatives for the familial deletion or duplication using test LDLM / Familial Hypercholesterolemia, LDLR Large Deletion/Duplication, Molecular Analysis

No LDLR large deletion or duplication detected.
- Interpretive report provided.

Note: If homozygous or compound heterozygous familial hypercholesterolemia is suspected based on clinical presentation, additional testing for a second pathogenic variant may be appropriate. The laboratory will contact the client and/or provider to discuss adjustment of this algorithm in appropriate cases.

*Approximately 15% of ADH is caused by pathogenic variants in the APOB gene. R3500Q and R3500W account for the majority of APOB pathogenic variant. It is more cost effective to rule out these 2 pathogenic variants first, then proceed to LDLR gene testing.
*Detects approximately 85%–90% of LDLR pathogenic variants.
*Detects approximately 10%–15% of LDLR pathogenic variants.