ARBORETUM CLINICAL
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LAB DIRECTOR
Owatha Tatum, Ph.D. HCLD/CC(ABB)
LABORATORY NAME
Arboretum Clinical, LLC

FIRST NAME: Oscar
LAST NAME: Meyer
DOB: 01/01/1964
PATIENT ID: HDHD-1-1

SAMPLE ID: ASDFG123
SAMPLE TYPE: Buccal swab
COLLECTION DATE: 01/06/2026
ORDERING PROVIDER: Sherlock Holmes

ORDERING PROVIDER CONTACT: 555-555-5555
ORDER REQUISITION: XXXXX
DATA RECEIVED: 01/08/2026
REPORT DATE: 01/18/2026

Arboretum Familial Hypercholesterolemia Test

Genes analyzed: LDLR, APOB, PCSK9, LDLRAP1

PRIMARY TEST RESULTS

POSITIVE - one pathogenic variant detected

One pathogenic variant was identified in the LDLR gene, associated with familial hypercholesterolemia.

GENE	VARIANT	PROTEIN CHANGE	ZYGOSITY	CLASSIFICATION
LDLR	c.2043C>A	p.Cys681Ter	Heterozygous	Pathogenic

PRIMARY TEST DETAIL

GENE LEVEL CONTEXT

LDLR, Heterozygous:
Pathogenic variants in LDLR are associated with autosomal dominant familial hypercholesterolemia. Individuals with heterozygous LDLR pathogenic variants typically present with LDL cholesterol levels 2-3 times above normal and are at significantly increased risk for premature atherosclerotic cardiovascular disease. [1,2,3]

INTERPRETATION AND EVIDENCE FOR VARIANT CLASSIFICATION

A stop gained variant was identified in LDLR (c.2043C>A; p.Cys681Ter). This variant is reported in ClinVar as "Pathogenic/Likely pathogenic" (status: "criteria provided, multiple submitters, no conflicts"; ID: 3699). This variant is present in gnomAD with a maximum population allele frequency of 8.25e-04, ~1 in 1,000 alleles. Loss of function is a known disease mechanism for this gene, and this stop gained variant is predicted to cause loss of function (PVS1). Functional studies support pathogenicity of this variant (PS3)[4]. This variant has been found more frequently in affected individuals than in unaffected controls (PS4)[5,6,7]. Based on this evidence, this variant has been classified as Pathogenic per ACMG/AMP guidelines.

FOLLOW UP RECOMMENDATIONS

It is recommended that these results are discussed with a certified genetic counselor or other healthcare professional with genetics expertise.

Results continued on next page

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PRIMARY TEST DETAIL (CONTINUED)

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TECHNICAL AND REGULATORY INFORMATION

GENE AND TRANSCRIPT PAIRS

GENE	TRANSCRIPT
LDLR	NM_000527.5
APOB	NM_000384.3
PCSK9	NM_174936.4
LDLRAP1	NM_015627.3

TEST METHODOLOGY

The Arboretum Familial Hypercholesterolemia Genetic Test is performed on genomic DNA extracted from buccal swabs, saliva, or whole blood. The test is validated for germline constitutional specimens only. Next-generation sequencing is performed using a blended approach combining low-coverage whole genome sequencing with high-coverage exome sequencing. Variant calling is performed using the DRAGEN Bio-IT Platform version 4.3.13 with alignment to reference genome GRCh38. Copy number variant detection utilizes the GATK germline CNV (gCNV) pipeline.

The test analyzes the genes listed above for sequence variants (single nucleotide variants, small insertions/deletions) and multi-exon copy number variants. Target regions include all coding exons and canonical splice site boundaries (±2bp). Variants are classified according to ACMG/AMP 2015 guidelines with familial hypercholesterolemia (FH)-specific modifications from the ClinGen Familial Hypercholesterolemia Variant Curation Expert Panel. Copy number variants are classified using 2020 ACMG/ClinGen CNV interpretation guidelines. Variants beyond the target regions are not reviewed nor classified as part of this test.

Only pathogenic and likely pathogenic variants are reported. Variants of uncertain significance (VUS), likely benign, and benign variants are not reported. The test is reported as positive when pathogenic and likely pathogenic variants are associated with the test phenotype, Familial Hypercholesterolemia. When pathogenic and likely pathogenic variants are found in the targeted genes associated with different phenotypes, they are reported as additional findings and this may include LDLRAP1 carrier status and APOB loss of function variants associated with hypobetalipoproteinemia. PCSK9 loss-of-function variants that are classified as benign and are protective and associated with reduced cardiovascular disease risk are not reported. Variants are reported using HGVS nomenclature.

Quality control acceptance criteria include: minimum mean coverage ≥20x across FH gene regions, overall genotype concordance ≥95%, and contamination estimate <5%. Samples not meeting these quality thresholds are not reported and may require recollection.

This sample and genetic data met Arboretum Clinical's quality standards for report generation.

TEST LIMITATIONS

The test does not assess polygenic risk or environmental factors that influence cholesterol levels and cardiovascular disease risk. A positive genetic result alone does not establish a diagnosis of familial hypercholesterolemia. Clinical correlation with lipid profiles, family history, and physical examination findings is required for diagnosis.

The assay does not detect single-exon copy number variants, deep intronic variants beyond splice site boundaries, variants in transcript isoforms, tissue-specific splicing variants, or variants in regulatory regions.

The assay does not detect complex structural variants including translocations or inversions and does not determine the precise structural configuration of duplications detected in the FH genes. Tandem duplications (which typically disrupt gene function and are pathogenic) cannot be distinguished from non-tandem duplications (which may preserve gene function). Consequently, detected partial-gene duplications cannot be definitively classified as pathogenic or benign based on structural characteristics alone and are classified as variants of uncertain significance (VUS) pending additional evidence from functional studies or alternative sequencing methodologies.

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A likely pathogenic or pathogenic result is identified in 20–40% of patients with a clinical diagnosis of FH.

This test was validated using samples from European, East Asian, and African ancestry populations. Variant interpretation relies on population frequency databases and computational prediction tools trained primarily on individuals of European ancestry. Performance may be reduced for individuals from populations with limited representation in genomic reference databases, including but not limited to Native American, Pacific Islander, and some Central Asian ancestries, or individuals with complex admixed ancestry.

When two or more pathogenic or likely pathogenic variants are detected in the same gene, chromosomal phase cannot be determined by this assay. For autosomal dominant genes (LDLR, APOB, PCSK9), clinical correlation with the patient's lipid profile can help distinguish between trans configuration (more severe phenotype) and cis configuration (typical heterozygous phenotype). For LDLRAP1 (autosomal recessive), clinical correlation is required to distinguish between trans configuration (disease-causing) and cis configuration (carrier status). Family segregation studies can definitively establish phase for any gene.

Individuals with significant germline mosaicism (>20% variant allele frequency deviation) may yield inaccurate variant calls. Bone marrow transplant recipients tested using blood-derived samples may reflect donor rather than recipient genotype; buccal swab specimens are recommended for transplant recipients.

Variant classifications may change as new scientific evidence becomes available. All detected variants are retained in laboratory records for potential reclassification.

LABORATORY INFORMATION

This test was performed by Arboretum Clinical, LLC, 6901 Quaker Ave. Ste B, Lubbock TX 79413 CLIA: 45D2331659, CAP: 7734236. Laboratory Director: Owatha Tatum, Ph.D., HCLD/CC(ABB). Sequencing services were provided by GenebyGene, Ltd., 1445 North Loop West, Suite 820 Houston, TX 77008, CLIA: 45D1102202, CAP: 7212851, Laboratory Director: Dr. Feng Zhou, PhD, HCLD(ABB), MB(ASCP). Both laboratories are authorized under the Clinical Laboratory Improvement Amendments (CLIA) to develop and perform high complexity clinical laboratory testing. This test was developed and its performance characteristics determined by Arboretum Clinical. It has not been cleared or approved by the U.S. Food and Drug Administration. It is a laboratory-developed test (LDT) not reviewed by the U.S. Food and Drug Administration.

RELEVANT RESOURCES

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