Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Familial Hypercholesterolemia Panel, Sequencing

ARUP test code 3002110

Familial Hypercholesterolemia Specimen	Whole Blood
Familial Hypercholesterolemia Interp	Positive

H=High, L=Low, *=Abnormal, C=Critical

RESULT
One pathogenic variant was detected in the LDLR gene.

PATHOGENIC VARIANT
Gene: LDLR (NM_000527.5)
Nucleic Acid Change: c.1783C>T; Heterozygous
Amino Acid Alteration: p.Arg595Trp
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1783C>T; p.Arg595Trp, was detected in the LDLR gene by massively parallel sequencing. Pathogenic variants in LDLR are associated with autosomal dominant familial hypercholesterolemia 1 and LDL cholesterol level QTL2 (MIM: 143890). This result is consistent with a diagnosis of familial hypercholesterolemia. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The LDLR c.1783C>T; p.Arg595Trp variant (rs373371572) is reported in the literature in several individuals affected with familial hypercholesterolemia (Leren 2021, Sturm 2021, Tada 2020). This variant is also reported as pathogenic by an expert panel in ClinVar (Variation ID: 161290) and is found in the non-Finnish European population with an allele frequency of 0.001548% (2/129168 alleles) in the Genome Aggregation Database. The arginine at codon 595 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.89). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should undergo cholesterol screening using a lipid panel and be offered testing for the identified pathogenic LDLR variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Leren TP et al. Molecular genetic testing for autosomal dominant hypercholesterolemia in 29,449 Norwegian index patients and 14,230 relatives during the years 1993-2020. Atherosclerosis. 2021 Apr;322:61-66. PMID: 33740630.
Sturm AC et al. Limited-Variant Screening vs Comprehensive Genetic Testing for Familial Hypercholesterolemia Diagnosis. JAMA Cardiol. 2021 Aug 1;6(8):902-909. PMID: 34037665
Tada H et al. A catalog of the pathogenic mutations of LDL receptor gene in Japanese familial hypercholesterolemia. J Clin Lipidol. 2020 May-Jun;14(3):346-351.e9. PMID: 32331935.

This result has been reviewed and approved by [redacted]

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BACKGROUND INFORMATION: Familial Hypercholesterolemia Panel, Sequencing

CHARACTERISTICS: Familial hypercholesterolemia (FH) is the most common inherited cardiovascular disease. It is characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) and premature atherosclerotic cardiovascular disease (ASCVD). Manifestations include coronary artery disease (CAD), cardiovascular disease (CVD), angina, myocardial infarction, xanthomas, and corneal arcus. Homozygous FH (HoFH) is a less common disorder, resulting from biallelic variants in a dominant FH-associated gene. HoFH is characterized by severe early-onset CAD, aortic stenosis, and high rate of coronary bypass surgery or death by teenage years.

EPIDEMIOLOGY: FH 1/250, HoFH 1/200,000 in the general population.

CAUSE: Pathogenic germline variants in genes associated with FH.

INHERITANCE: Autosomal dominant for LDLR, APOB and PCSK9-associated FH. Autosomal recessive for LDLRAP1-associated FH. HoFH results from biallelic variants in an autosomal dominant FH gene.

PENETRANCE: Estimated at 73-90 percent in individuals with molecularly confirmed FH; influenced by gene, variant, and non-genetic factors.

CLINICAL SENSITIVITY: Up to 85 percent for FH.

GENES TESTED: APOB, LDLR, LDLRAP1, PCSK9.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of FH. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants, deep intronic variants, and large deletions/duplications/inversions will not be identified. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Familial Hypercholesterolemia Specimen	22-301-104626	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Familial Hypercholesterolemia Interp	22-301-104626	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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