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

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/8/2021
Gender:	Female
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

INDICATION FOR TESTING
Hypercholesterolemia

RESULT
One pathogenic variant was detected in the LDLR gene.

PATHOGENIC VARIANT
Gene: LDLR (NM_000527.4)
Nucleic Acid Change: c.11G>A; Heterozygous
Amino Acid Alteration: p.Trp4Ter
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.11G>A; p.Trp4Ter, was detected in the LDLR gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic LDLR variants are inherited in an autosomal dominant manner, and are associated with familial hypercholesterolemia (FH), type I (MIM: 143890). This result is consistent with the diagnosis of FH, type I. Future offspring of this individual have a 50 percent chance of inheriting this pathogenic variant.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and the limitations of this test.

Evidence for variant classification:
The LDLR c.11G>A; p.Trp4Ter variant (rs201016593), also known as p.Trp-18Ter, is reported in the literature as Class I mutation in multiple individuals with elevated levels of plasma total and LDL cholesterol (Garcia-Garcia 2011, Hobbs 1992, Olfson 2015, Orita 1989). This variant is reported as pathogenic in ClinVar (Variation ID: 250973). This variant is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. 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 Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report.

REFERENCES
Garcia-Garcia AB et al. Reduced penetrance of autosomal dominant hypercholesterolemia in a high percentage of families: importance of genetic testing in the entire family. Atherosclerosis. 2011 218:423-430.

Hobbs HH et al. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Hum Mutat. 1992 1:445-466.

Olfson E et al. Identification of Medically Actionable Secondary Findings in the 1000 Genomes. PLoS One. 2015 10:e0135193.

Orita M et al. Rapid and sensitive detection of point mutations and DNA polymorphisms using the polymerase chain reaction. Genomics. 1989 5:874-879.

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Familial Hypercholesterolemia Specimen	21-069-104070	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Familial Hypercholesterolemia Interp	21-069-104070	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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