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

Loeys-Dietz Syndrome Core Panel, Sequencing

ARUP test code 3003947

Spcm LDS	Whole Blood
LDS Interp	Positive

RESULT
One pathogenic variant was detected in the TGFBR1 gene.

PATHOGENIC VARIANT
Gene: TGFBR1 (NM_004612.2)
Nucleic Acid Change: c.1460G>A; Heterozygous
Amino Acid Alteration: p.Arg487Gln
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.1460G>A; p.Arg487Gln, was detected in the TGFBR1 gene by massively parallel sequencing. This result is consistent with a diagnosis of Loeys-Dietz syndrome; clinical manifestations are highly variable and may be age-dependent. This individual's offspring have a 50 percent chance of inheriting the causative 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 TGFBR1 c.1460G>A; p.Arg487Gln variant (rs113605875) is reported in the literature, including de novo occurrences, in several individuals affected with Loeys-Dietz syndrome acute aortic dissection, and thoracic aortic aneurysms (Frischmeyer-Guerrerio 2013, Goudie 2011, Mariucci 2020, Matyas 2006, Overwater 2018). This variant is also reported in ClinVar (Variation ID: 12525), but is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. The arginine at codon 487 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.900). In vitro functional analyses demonstrate decreased expression and signaling (Goudie 2011). Additionally, other amino acid substitutions at this codon (Trp, Gly, Pro) have been reported in individuals with Loeys-Dietz syndrome (Frischmeyer-Guerrerio 2013, Goudie 2011). Based on available information, the p.Arg487Gln variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic TGFBR1 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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

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
Frischmeyer-Guerrerio PA et al. TGFbeta receptor mutations impose a strong predisposition for human allergic disease. Sci Transl Med. 2013 Jul 24;5(195):195ra94. PMID: 23884466.
Goudie DR et al. Multiple self-healing squamous epithelioma is caused by a disease-specific spectrum of mutations in TGFBR1. Nat Genet. 2011 Feb 27;43(4):365-9. PMID: 21358634.
Mariucci E et al. Aortic arch geometry predicts outcome in patients with Loeys-Dietz syndrome independent of the causative gene. Am J Med Genet A. 2020 Jul;182(7):1673-1680. PMID: 32352226.
Matyas G et al. Identification and in silico analyses of novel TGFBR1 and TGFBR2 mutations in Marfan syndrome-related disorders. Hum Mutat. 2006 Aug;27(8):760-9. PMID: 16791849.
Overwater E et al. Results of next-generation sequencing gene panel diagnostics including copy-number variation analysis in 810 patients suspected of heritable thoracic aortic disorders. Hum Mutat. 2018 Sep;39(9):1173-1192. PMID: 29907982.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Loeys-Dietz Syndrome Core Panel, Sequencing

CHARACTERISTICS: Cardiovascular findings (aortic dissection, arterial aneurysms, arterial tortuosity, MVP), skeletal abnormalities (arachnodactyly, talipes equinovarus, joint laxity, cervical spine malformations and instability, pectus excavatum and carinatum), craniofacial features (hypertelorism, retrognathia, craniosynostosis, and bifid uvula), cutaneous findings (translucent velvety skin, visible veins in chest, widened poorly-formed scars, and easy bruising), allergy and gastrointestinal disease (asthma, allergic rhinitis, food allergy, eosinophilic gastrointestinal disease) and spontaneous rupture of spleen, bowel, and uterus during pregnancy).

EPIDEMIOLOGY: Unknown.

CAUSE: Pathogenic germline variants in SMAD2, SMAD3, TGFB2, TGFB3, TGFBR1, and TGFBR2.

INHERITANCE: Autosomal dominant; 75 percent of cases are caused by a de novo variant.

PENETRANCE: High

CLINICAL SENSITIVITY: Approximately 75-85 percent.

GENES TESTED: TGFBR1, TGFBR2.

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 confirm reported variants.

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 Loeys-Dietz syndrome. This test only detects variants within the coding regions and intron-exon boundaries of the TGFBR1 and TGFBR2 genes. Variants in other genes, causing LDS (SMAD2, SMAD3, TGFB2, TGFB3) are not analyzed by this core panel. Regulatory region variants and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massively 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. Noncoding 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
Spcm LDS	22-307-111835	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
LDS Interp	22-307-111835	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