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

Physician: Doctor, Example

Patient: Patient, Example

DOB	1/7/1979
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Dilated Cardiomyopathy Panel, Sequencing

ARUP test code 3001581

Dilated Cardiomyopathy Specimen	Whole Blood
Dilated Cardiomyopathy Interp	Positive

RESULT
One likely pathogenic variant was detected in the DSP gene.

LIKELY PATHOGENIC VARIANT
Gene: DSP (NM_004415.4)
Nucleic Acid Change: c.6466dup; Heterozygous
Amino Acid Alteration: p.Arg2156LysfsTer9
Inheritance: Autosomal dominant/recessive

INTERPRETATION
One likely pathogenic variant, c.6466dup; p.Arg2156LysfsTer9, was detected in the DSP gene by massively parallel sequencing. Pathogenic variants in DSP are associated with autosomal dominant arrhythmogenic right ventricular dysplasia 8 (MIM: 607450), dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis (MIM: 615821), and keratosis palmoplantaris striata II (MIM: 612908), and autosomal recessive dilated cardiomyopathy with woolly hair and keratoderma (MIM: 605676), lethal acantholytic epidermolysis bullosa (MIM: 609638), and skin fragility-woolly hair syndrome (MIM: 607655; OMIM(R)). This result is consistent with a diagnosis of a dominant DSP-associated disorder. This individual's offspring have a 50 percent chance of inheriting the likely 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 DSP c.6466dup; p.Arg2156LysfsTer9 variant (rs1554108859, ClinVar Variation ID: 419496) is reported in the literature in one individual from a genomic screening cohort who did not report arrhythmogenic cardiomyopathy (ACM); however, a portion of individuals in this cohort exhibited some features of ACM (Carruth 2021). This variant is absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This variant results in a premature termination codon in the last exon of the DSP gene. While this may not lead to nonsense-mediated decay, it is expected to create a truncated DSP protein. Additionally, several downstream truncating variants have been described in individuals with cardiomyopathy and are considered pathogenic (Castelletti 2017, Smith 2020). Based on available information, this variant is considered to be likely pathogenic.

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

RECOMMENDATIONS
Cardiology and genetic consultations are indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified likely pathogenic DSP 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
Carruth ED et al. Clinical Findings and Diagnostic Yield of Arrhythmogenic Cardiomyopathy Through Genomic Screening of Pathogenic or Likely Pathogenic Desmosome Gene Variants. Circ Genom Precis Med. 2021 Apr;14(2):e003302. PMID: 33684294.
Castelletti et al. Desmoplakin missense and non-missense mutations in arrhythmogenic right ventricular cardiomyopathy: Genotype-phenotype correlation. Int J Cardiol. 2017 Dec 15;249:268-273. PMID: 28527814.

Smith et al. Desmoplakin Cardiomyopathy, a Fibrotic and Inflammatory Form of Cardiomyopathy Distinct From Typical Dilated or Arrhythmogenic Right Ventricular Cardiomyopathy. Circulation. 2020 Jun 9;141(23):1872-1884. PMID: 32372669

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Dilated Cardiomyopathy Panel, Sequencing

CHARACTERISTICS: Dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement with systolic dysfunction. DCM is a leading cause of symptoms requiring heart transplantation in children and adults. Familial DCM is defined as two or more individuals in single family with DCM, or an individual with DCM with a relative with unexplained sudden death less than 35 years of age. Affected individuals are at risk for heart failure, arrhythmias or conduction disease, pregnancy-related cardiomyopathy, stroke, and sudden cardiac death. Symptoms may include dyspnea, chest pain, palpitations, fatigue, fainting or edema. Syndromic forms of DCM include extracardiac manifestations.
EPIDEMIOLOGY: Prevalence of DCM is estimated at 1:250 to 1:2500; 20-50 percent of cases are familial.
CAUSE: Pathogenic germline variants in genes associated with familial DCM.

INHERITANCE: Typically autosomal dominant for familial DCM. Genes with X-linked, autosomal recessive, and mitochondrial inheritance also associated. De novo variation, compound heterozygous, or digenic heterozygous variants have been reported.
PENETRANCE: Variable.
CLINICAL SENSITIVITY: 25-40 percent for familial DCM, 10-25 percent for isolated DCM.
GENES TESTED: ABCC9, ACTC1, ACTN2, ALMS1, BAG3, CRYAB, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, EMD, FKTN, FLNC*, GLA, JUP, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, PKP2, PLN, PRDM16, PRKAG2*, RAF1, RBM20, RYR2, SCN5A, SGCD, TAZ, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTN*, TTR, VCL.

* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

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. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable form of DCM. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Mitochondrial (mtDNA) genes are not interrogated. Regulatory region variants, large deletions/duplications/inversions and deep intronic variants 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 are not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
FLNC(NM_001458) exons 47, 48
PRKAG2(NM_016203) exons 10, 13
TTN(NM_001267550) exons 172, 173, 175, 176, 177, 178, 179, 180, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 215
TTN(NM_133378) exons 153, 154, 155

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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Dilated Cardiomyopathy Specimen	24-276-128307	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Dilated Cardiomyopathy Interp	24-276-128307	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