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

Physician: Doctor, Example

Patient: Patient, Example

DOB	5/26/1961
Gender:	Female
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 pathogenic variant was detected in the MYH7 gene. One variant of uncertain significance was detected in the DSP gene.

PATHOGENIC VARIANT
Gene: MYH7 (NM_000257.4)
Nucleic Acid Change: c.2389G>A; Heterozygous
Amino Acid Alteration: p.Ala797Thr
Inheritance: Autosomal dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: DSP (NM_004415.4)
Nucleic Acid Change: c.620G>C; Heterozygous
Amino Acid Alteration: p.Trp207Ser
Inheritance: Autosomal dominant/recessive

INTERPRETATION
One pathogenic variant, c.2389G>A; p.Ala797Thr, was detected in the MYH7 gene by massively parallel sequencing. Pathogenic variants in MYH7 are associated with autosomal dominant dilated cardiomyopathy 1S (MIM: 613426), hypertrophic cardiomyopathy 1 (MIM: 192600), left ventricular noncompaction 5 (MIM: 613426), Laing distal myopathy (MIM: 160500), myosin storage myopathy (MIM: 608358), myopathic type scapuloperoneal syndrome (MIM: 181430), and autosomal recessive myosin storage myopathy (MIM: 255160). This result is consistent with a diagnosis of a MYH7-related disorder. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

One variant of uncertain clinical significance, c.620G>C; p.Trp207Ser, 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). However, it is uncertain whether this variant is disease-associated or benign.

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

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

Evidence for variant classifications:
The MYH7 c.2389G>A; p.Ala797Thr variant (rs3218716; ClinVar Variation ID: 42901), also known as A797T, is a known founder variant in Black South African population (Moolman-Smook 2002). This variant has been shown to co-segregated with disease in multiple individuals and has been identified in multiple unrelated individuals (selected references: Moolman-Smook 2000, Mattos 2016, Walsh 2017). This variant is associated with mild-moderate hypertrophic cardiomyopathy and displays incomplete penetrance (Moolman-Smook 2000). Based on available information, this variant is considered to be pathogenic.

The DSP c.620G>C; p.Trp207Ser variant (rs1445705079), to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 1512144). This variant is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism, but is considered a low confidence variant in the database. Computational analyses predict that this variant is deleterious (REVEL: 0.933). However, given the lack of clinical and functional data, the significance of this variant is uncertain at this time.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. Genetic and cardiology consultations are recommended. At-risk family members should be offered testing for the identified pathogenic MYH7 variant (Familial Targeted Sequencing, ARUP test code 3005867). Surveillance of the literature for new information concerning the uncertain variant is recommended.

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
Mattos BP et al. Prevalence and Phenotypic Expression of Mutations in the MYH7, MYBPC3 and TNNT2 Genes in Families with Hypertrophic Cardiomyopathy in the South of Brazil: A Cross-Sectional Study. Arq Bras Cardiol. 2016 Sep;107(3):257-265. PMID: 27737317.

Moolman-Smook J et al. Expression of HCM causing mutations: lessons learnt from genotype-phenotype studies of the South African founder MYH7 A797T mutation. J Med Genet. 2000 Dec;37(12):951-6. PMID: 11186938.

Walsh R et al. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. Genet Med. 2017 Feb;19(2):192-203. PMID: 27532257.

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Dilated Cardiomyopathy Specimen	23-069-402099	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Dilated Cardiomyopathy Interp	23-069-402099	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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