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

Physician: Doctor, Example

Patient: Patient, Example

DOB	7/9/1962
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication

ARUP test code 2010183

Cardiomyopathy/Arrhythmia Panel Specimen	Whole Blood

Cardiomyopathy/Arrhythmia Panel Interp

Positive

INDICATION FOR TESTING
Patient with ARVC

RESULT
One likely pathogenic variant was detected in the DSG2 gene. Three variants of uncertain significance were detected, one each in the DSG2, DSP, and LDB3 genes.

LIKELY PATHOGENIC VARIANT
Gene: DSG2 (NM_001943.4)
Nucleic Acid Change: c.3059_3062delAGAG Heterozygous
Amino Acid Alteration: p.Glu1020AlafsTer18
Inheritance: Autosomal dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: DSG2 (NM_001943.4)
Nucleic Acid Change: c.874C>T; Heterozygous
Amino Acid Alteration: p.Arg292Cys
Inheritance: Autosomal dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: DSP (NM_004415.3)
Nucleic Acid Change: c.2684A>G; Heterozygous
Amino Acid Alteration: p.Tyr895Cys
Inheritance: Autosomal dominant/ Autosomal recessive

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: LDB3 (NM_007078.2)
Nucleic Acid Change: c.566C>T; Heterozygous
Amino Acid Alteration: p.Ser189Leu
Inheritance: Autosomal dominant

INTERPRETATION
One copy of a likely pathogenic variant, c.3059_3062delAGAG; p.Glu1020AlafsTer18, was detected in the DSG2 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic variants in DSG2 are associated with autosomal dominant arrhythmogenic right ventricular dysplasia 10 (MIM: 610193) and dilated cardiomyopathy 1BB (MIM: 612877). This result is consistent with a diagnoses of arrhythmic right ventricular cardiomyopathy. Offspring of this individual have a 50 percent chance of inheriting the causative variant.

Additionally, one copy of a variant of uncertain clinical significance, c.874C>T; p.Arg292Cys, was detected in the DSG2

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

gene by massively parallel sequencing. Pathogenic variants in DSG2 are associated with autosomal dominant arrhythmogenic right ventricular dysplasia 10 (MIM: 610193) and dilated cardiomyopathy 1BB (MIM: 612877). If this variant is later determined to be pathogenic, this patient would be predicted to be affected.

One copy of a variant of uncertain clinical significance, c.2684A>G; p.Tyr895Cys, was detected in the DSP gene by massively parallel sequencing. Pathogenic variants in the DSP gene are associated with autosomal dominant arrhythmogenic right ventricular dysplasia 8 (MIM: 607450), dilated cardiomyopathy with woolly hair keratoderma and tooth agenesis (MIM: 615821), and with 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). If this variant is later determined to be pathogenic, this patient would be predicted to be affected.

One copy of a variant of uncertain clinical significance, c.566C>T; p.Ser189Leu, was detected in the LDB3 gene by massively parallel sequencing. Pathogenic variants in LDB3 are inherited in an autosomal dominant manner, and are associated with myofibrillar myopathy 4 (MIM: 609452) and dilated cardiomyopathy 1C, with or without LVNC, hypertrophic cardiomyopathy 24, and left ventricular noncompaction 3 (MIM: 601493). If this variant is later determined to be pathogenic, this patient would be predicted to be affected.

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

Evidence for variant classification:
The DSG2 c.3059_3062delAGAG; p.Glu1020AlafsTer18 variant (rs397516706) is reported in the literature in multiple individuals with arrhythmogenic right ventricular cardiomyopathy (Christensen 2010, Rasmussen 2013). In addition, this variant was also observed to partially segregate with disease in a family with ARVC (Lahtinen 2011). This variant is also reported in ClinVar (Variation ID: 199827) and is found in the general population with an overall allele frequency of 0.004% (9/249404 alleles) in the Genome Aggregation Database. This variant results in a premature termination codon in the last exon of the DSG2 gene. While this variant has been shown to escape nonsense-mediated decay, it is expected to create a truncated protein disrupting the last 99 amino acids (Rasmussen 2013). Based on available information, this variant is considered to be likely pathogenic.

The DSG2 c.874C>T; p.Arg292Cys variant (rs770921270) is reported in the literature in several individuals affected with arrhythmogenic right ventricular dysplasia/cardiomyopathy including multiple instances of homozygosity (Cox 2011, Sato 2011, Nakajima 2012, Wada 2017, Walsh 2017). This variant is reported in ClinVar (Variation ID: 466351). This variant is found in the general population with an overall allele frequency of 0.005% (12/249360 alleles) in the Genome Aggregation Database. The arginine at codon 292 is highly conserved, but computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.362). However, given the lack of clinical and functional data, the significance of the p.Arg292Cys variant is uncertain at this time.

The DSP c.2684A>G; p.Tyr895Cys variant (rs367752002) is reported in the literature in an individual affected with arrhythmogenic right ventricular cardiomyopathy (Caforio 2020). This variant is also reported in ClinVar (Variation ID: 163257). This variant is found in the general population with an overall allele frequency

of 0.016% (44/282708 alleles) in the Genome Aggregation Database. The tyrosine at codon 895 is moderately conserved, and computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.212). However, given the lack of clinical and functional data, the significance of the p.Tyr895Cys variant is uncertain at this time.

The LDB3 c.566C>T; p.Ser189Leu variant (rs45487699), also known as S196L in the literature, is reported in two probands affected with dilated cardiomyopathy (DCM), three with hypertrophic cardiomyopathy, and one with ventricular tachycardia (Haas 2014, Leinonen 2018, Mook 2013, Theis 2006, Vatta 2003). This variant segregated with DCM in four affected relatives of one of the probands with DCM. Functional studies suggest that the p.Ser189Leu variant alters activity of the protein encoded by LDB3, and a mouse model expressing this variant protein in cardiac tissue developed DCM (Arimura 2009 and Li 2010). This variant is also reported in ClinVar (Variation ID: 4731). This variant is found in the general population with an allele frequency of 0.061% (173/281,154 alleles) in the Genome Aggregation Database, which is higher than expected for a pathogenic variant. The serine at codon 189 is weakly conserved, but computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.183). However, due to conflicting information, the clinical significance of this variant is uncertain at this time.

RECOMMENDATIONS
Genetic consultation is recommended, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified likely pathogenic DSG2 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Surveillance of the literature for new information concerning the uncertain variants 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 included in this report.

REFERENCES
Arimura et al. Impaired Binding of ZASP/Cypher With Phosphoglucomutase 1 Is Associated With Dilated Cardiomyopathy. Cardiovasc Res. 2009 Jul 1;83(1):80-8. PMID: 19377068.

Caforio ALP et al. Evidence From Family Studies for Autoimmunity in Arrhythmogenic Right Ventricular Cardiomyopathy: Associations of Circulating Anti-Heart and Anti-Intercalated Disk Autoantibodies With Disease Severity and Family History. Circulation. 2020 Apr 14;141(15):1238-1248. PMID: 32114801.

Christensen AH et al. Wide spectrum of desmosomal mutations in Danish patients with arrhythmogenic right ventricular cardiomyopathy. J Med Genet. 2010 Nov;47(11):736-44. PMID: 20864495.

Cox MG et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: pathogenic desmosome mutations in index-patients predict outcome of family screening: Dutch arrhythmogenic right ventricular dysplasia/cardiomyopathy genotype-phenotype follow-up study. Circulation. 2011 Jun 14;123(23):2690-700. PMID: 21606396.

Haas et al. Atlas of the Clinical Genetics of Human Dilated Cardiomyopathy. Eur Heart J. 2015 May 7;36(18):1123-35a. PMID: 25163546.

Lahtinen AM et al. Population-prevalent desmosomal mutations predisposing to arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm. 2011 Aug;8(8):1214-21. PMID: 21397041.

Leinonen et al. The Genetics Underlying Idiopathic Ventricular Fibrillation: A Special Role for Catecholaminergic Polymorphic Ventricular Tachycardia? Int J Cardiol. 2018 Jan 1;250:139-145. PMID: 29032884.

Li et al. A ZASP Missense Mutation, S196L, Leads to Cytoskeletal and Electrical Abnormalities in a Mouse Model of Cardiomyopathy. Circ Arrhythm Electrophysiol. 2010 Dec;3(6):646-56. PMID: 20852297.

Mook et al. Targeted Sequence Capture and GS-FLX Titanium Sequencing of 23 Hypertrophic and Dilated Cardiomyopathy Genes: Implementation Into Diagnostics. J Med Genet. 2013 Sep;50(9):614-26. PMID: 23785128.

Rasmussen TB et al. Mutated desmoglein-2 proteins are incorporated into desmosomes and exhibit dominant-negative effects in arrhythmogenic right ventricular cardiomyopathy. Hum Mutat. 2013 May;34(5):697-705. PMID: 23381804.

Sato T et al. Sudden death during exercise in a juvenile with arrhythmogenic right ventricular cardiomyopathy and desmoglein-2 gene substitution: a case report. Leg Med (Tokyo). 2011 Nov;13(6):298-300. PMID: 22000064.

Theis et al. Echocardiographic-determined Septal Morphology in Z-disc Hypertrophic Cardiomyopathy. Biochem Biophys Res Commun. 2006 Dec 29;351(4):896-902. PMID: 17097056.

Nakajima T et al. Compound and digenic heterozygosity in desmosome genes as a cause of arrhythmogenic right ventricular cardiomyopathy in Japanese patients. Circ J. 2012;76(3):737-43. PMID: 22214898.

Vatta et al. Mutations in Cypher/ZASP in Patients With Dilated Cardiomyopathy and Left Ventricular Non-Compaction. J Am Coll Cardiol. 2003 Dec 3;42(11):2014-27. PMID: 14662268.

Wada Y et al. Unique genetic background and outcome of non-Caucasian Japanese probands with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Mol Genet Genomic Med. 2017 Nov;5(6):639-651. PMID: 29178656.

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: Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Inherited cardiomyopathy and arrhythmia disorders are genetically and phenotypically heterogeneous. Phenotypes include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction (LVNC), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), long QT syndrome (LQTS), and short QT syndrome (SQTS).

EPIDEMIOLOGY: The prevalence of HCM is 1 in 500, DCM is greater than 1 in 500, ARVC is 1 in 1000, LQTS is 1 in 3,000, CPVT is 1 in 10,000, and it is unknown for BrS, LVNC, and SQTS.

CAUSE: Pathogenic germline variants in genes associated with cardiomyopathy and arrhythmia such as nuclear genes encoding sarcomeric or desmosomal proteins, cardiac ion channel components and cytoskeletal proteins, or pathogenic variants within the mitochondrial genome.

INHERITANCE: Is gene dependent and can be autosomal recessive, autosomal dominant, X-linked or mitochondrial.

PENETRANCE: Variable; dependent on gene and variant.

CLINICAL SENSITIVITY: Dependent on clinical phenotype. Estimated at 50 percent for ARVC, 15-30 percent for BrS, 60 percent for CPVT, 30-40 percent for DCM, 50-60 percent for non-syndromic familial HCM, and 60-75 percent for LQTS.

GENES TESTED: ABCC9, ACTC1, ACTN2, ANK2, ANKRD1, BAG3**, CACNA1C, CACNB2, CASQ2, CAV3, CRYAB**, CSRP3, DES, DMD, DSC2, DSG2, DSP, DTNA, EMD**, EYA4, FHL1**, FKRP, FKTN, GAA, GATAD1**, GLA, GPD1L, JPH2, JUP, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNQ1, LAMA4, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOT, MYOZ2, MYPN, NEXN, PKP2, PLN, PRKAG2, RBM20, RYR2, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SGCA, SGCB, SGCD, SGCG, SLC25A4, SNTA1, TAZ**, TCAP, TGFB3, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TRDN**, TRPM4, TTN*, TTR, VCL

* One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
** Deletion/duplication detection is not available for this gene.

METHODOLOGY: Targeted 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. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: 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 heritable form of cardiomyopathy or arrhythmia. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Variants in the mitochondrial genome are not detected. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. 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 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.

The following regions are not sequenced due to technical limitations of the assay:
TTN(NM_001267550) exon(s) 172,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,215
TTN(NM_133378) exon(s) 153,154,155

Single exon deletions/duplications will not be called for the following exons:
ACTN2(NM_001103) 17; CACNB2(NM_001167945) 7; DMD(NM_000109) 1; DSC2(NM_024422) 1; DTNA(NM_001390) 16,21; KCNH2(NM_000238) 13;

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

KCNQ1(NM_000218) 16; KCNQ1(NM_181798) 1; MYBPC3(NM_000256) 10,24; MYH6(NM_002471) 24,28; MYH7(NM_000257) 29; PKP2(NM_004572) 6; PRKAG2(NM_001304527) 1; PRKAG2(NM_001304531) 2; PRKAG2(NM_016203) 5; SGCB(NM_000232) 1; SGCG(NM_000231) 8; TGFB3(NM_003239) 7; TRPM4(NM_001321285) 4; TRPM4(NM_017636) 7; TTN(NM_001267550) 158,173,176,185,191,194;TTN(NM_133378) 114,148,155,156,167,170

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
Cardiomyopathy/Arrhythmia Panel Specimen	21-079-400545	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cardiomyopathy/Arrhythmia Panel Interp	21-079-400545	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