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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/30/1981
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

RESULT
One pathogenic variant was detected in the MYBPC3 gene.

PATHOGENIC VARIANT
Gene: MYBPC3 (NM_000256.3)
Nucleic Acid Change: c.821+1G>A; Heterozygous
Inheritance: Autosomal dominant/recessive

INTERPRETATION
One pathogenic variant, c.821+1G>A; , was detected in the MYBPC3 gene by massively parallel sequencing. Pathogenic variants in MYBPC3 are associated with autosomal dominant dilated cardiomyopathy 1MM and left ventricular noncompaction 10 (MIM: 615396) and autosomal dominant or recessive hypertrophic cardiomyopathy 4 (MIM: 115197; OMIM(R)). This result is consistent with a diagnosis of MYBPC3-associated cardiomyopathy. This individual's offspring have a 50 percent chance of inheriting the 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 MYBPC3 c.821+1G>A variant (rs397516073), also known as IVS7+1G>A and Int8DSG+1A, is reported in the literature in multiple individuals affected with hypertrophic cardiomyopathy and segregated with disease in multiple families (Erdmann 2001, Maron 2001, Murphy 2016, Van Driest 2004). This variant is also reported in ClinVar (Variation ID: 42791) and is found in the general population with an allele frequency of 0.003% (5/172994 alleles) in the Genome Aggregation Database (v2.1.1). This variant disrupts the canonical splice donor site of intron 7, and experimental evidence found this variant leads to two aberrant transcripts with skipping of either exon 7 alone or skipping of exons 7 and 8. Both transcripts lead to premature stop codons in exon 9 (Erdmann 2001). Based on available information, this variant is considered to be pathogenic.

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 pathogenic MYBPC3 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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

COMMENTS
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
Erdmann J et al. Spectrum of clinical phenotypes and gene variants in cardiac myosin-binding protein C mutation carriers with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2001 Aug;38(2):322-30. PMID: 11499719.
Maron BJ et al. Development of left ventricular hypertrophy in adults in hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. J Am Coll Cardiol. 2001 Aug;38(2):315-21. PMID: 11499718.
Murphy SL et al. Evaluation of the Mayo Clinic Phenotype-Based Genotype Predictor Score in Patients with Clinically Diagnosed Hypertrophic Cardiomyopathy. J Cardiovasc Transl Res. 2016 Apr;9(2):153-61. PMID: 26914223.
OMIM(R) Copyright (C) 1996 - Present year, Johns Hopkins University. All rights reserved.
Van Driest SL et al. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004 Nov 2;44(9):1903-10. PMID: 15519027.

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 1 in 250 to 1 in 2,500, ARVC is 1 in 1,000, LQTS is 1 in 2,500, 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: 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, 25-40 percent for familial DCM, 50-60 percent for nonsyndromic familial HCM, and 60-75 percent for LQTS.

GENES TESTED: ABCC9; ACTC1; ACTN2; AGL; ALMS1; ALPK3; BAG3; BRAF*; CACNA1C; CALM1*; CALM2; CALM3; CASQ2; CRYAB; CSRP3*; DES*; DMD; DOLK; DSC2; DSG2; DSP; EMD; FHL1*; FKTN*; FLNC*; GAA; GLA; HCN4; HRAS; JPH2; JUP; KCNE1; KCNE2; KCNH2*; KCNJ2; KCNQ1; KRAS; LAMP2; LDB3; LMNA; MAP2K1; MAP2K2*; MYBPC3; MYH6*; MYH7*; MYL2; MYL3; NEXN; NKX2-5; NRAS; PKP2*; PLN; PRDM16; PRKAG2*; PTPN11**; RAF1*; RBM20; RIT1*; RYR2; SCN5A; SOS1*; TAFAZZIN; TCAP; TECRL*; TMEM43; TNNC1; TNNI3; TNNI3K; TNNT2; TPM1*; TRDN*; TTN*; TTR; VCL

*One or more exons are not covered by sequencing and/or deletion duplication analysis for the indicated gene; see limitations section below.

**Deletion/duplication detection is not available for this gene.

METHODOLOGY: Probe hybridization-based 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 that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

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. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
BRAF (NM_004333, NM_001378468, NM_001378469, NM_001378473, NM_001378474) exon(s) 5,18
BRAF (NM_001354609, NM_001378472, NM_001378467) exon(s) 5,18,19
BRAF (NM_001374244) exon(s) 5,10,19
BRAF (NM_001374258) exon(s) 5,10,19,20
BRAF (NM_001378470, NM_001378475) exon(s) 4,17,18
BRAF (NM_001378471) exon(s) 5,17,18
CALM1 (NM_001363670) exon(s) 1
CSRP3 (NM_001369404) partial exon(s) 5(Chr11:19204180-19204196)
DES (NM_001382712) exon(s) 9
FKTN (NM_001351497) exon(s) 6
FKTN (NM_001351498) partial exon(s) 9(Chr9:108382363-108382373)
FLNC (NM_001458) exon(s) 47,48
FLNC (NM_001127487) exon(s) 46,47
PRKAG2 (NM_016203, NM_001040633) exon(s) 13
PRKAG2 (NM_001304527, NM_001363698) exon(s) 11
PRKAG2 (NM_001304531) exon(s) 10
PRKAG2 (NM_024429) exon(s) 9
RAF1 (NM_001354689) exon(s) 8

RAF1 (NM_001354694) exon(s) 7
SOS1 (NM_001382394) exon(s) 1
TECRL (NM_001363796) exon(s) 12
TPM1 (NM_001365777) partial exon(s) 9(Chr15:63358119-63358186)
TPM1 (NM_001365780) partial exon(s) 8(Chr15:63358119-63358186)
TTN (NM_001267550) exon(s)
172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,1
88,189,190,191,192,193,194,195,196,197
TTN (NM_001256850) exon(s) 154,155,156
TTN (NM_133378) exon(s) 153,154,155

Single exon deletions/duplications will not be called for the following exons:
BRAF (NM_004333) 3,18; BRAF (NM_001354609) 3,18-19; BRAF (NM_001374244) 3,10,19; BRAF (NM_001374258) 3,10,19-20; BRAF (NM_001378467) 3,18-19; BRAF (NM_001378468) 3,18; BRAF (NM_001378469) 3,18; BRAF (NM_001378470) 2,17-18; BRAF (NM_001378471) 3,17-18; BRAF (NM_001378472) 3,18-19; BRAF (NM_001378473) 3,18; BRAF (NM_001378474) 3,18; BRAF (NM_001378475) 17-18; CALM1 (NM_001363670) 1; DES (NM_001382712) 9; FHL1 (NM_001449) 7; FHL1 (NM_001159699) 6; FHL1 (NM_001159700) 7; FHL1 (NM_001159701) 6; FHL1 (NM_001159702) 8; FHL1 (NM_001159703) 6; FHL1 (NM_001159704) 6; FHL1 (NM_001167819) 7; FHL1 (NM_001330659) 5; FHL1 (NM_001369326) 8; FHL1 (NM_001369327) 8; FHL1 (NM_001369328) 8; FHL1 (NM_001369329) 7; FHL1 (NM_001369330) 7; FHL1 (NM_001369331) 6; FKTN (NM_001351497) 6; FLNC (NM_001458) 44-48; FLNC (NM_001127487) 43-47; KCNH2 (NM_000238) 6; KCNH2 (NM_001204798) 2; KCNH2 (NM_172056) 6; KCNH2 (NM_172057) 2; MAP2K2 (NM_030662) 1; MYH6 (NM_002471) 26; MYH7 (NM_000257) 27; PKP2 (NM_004572) 1; PKP2 (NM_001005242) 1; PRKAG2 (NM_016203) 13; PRKAG2 (NM_001040633) 13; PRKAG2 (NM_001304527) 11; PRKAG2 (NM_001304531) 10; PRKAG2 (NM_001363698) 11; PRKAG2 (NM_024429) 9; RAF1 (NM_001354689) 8; RAF1 (NM_001354694) 7; RIT1 (NM_001256821) 1; SOS1 (NM_001382394) 1; TECRL (NM_001363796) 12; TRDN (NM_006073) 5; TRDN (NM_001251987) 5; TRDN (NM_001256020) 5; TRDN (NM_001256021) 5; TRDN (NM_001256022) 5; TTN (NM_001267550) 172-197,201; TTN (NM_001256850) 154-156; TTN (NM_133378) 153-155

This test was developed and its performance characteristics determined by ARUP Laboratories. The U.S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

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
Cardiomyopathy/Arrhythmia Panel Specimen	25-048-400618	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cardiomyopathy/Arrhythmia Panel Interp	25-048-400618	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