Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: ARUP,

Patient: REPORT, POSITIVE

DOB	4/20/2021
Gender:	Female
Patient Identifiers:	29768
Visit Number (FIN):	30073
Collection Date:	4/22/2021 13:44

Dilated Cardiomyopathy Panel, Sequencing

ARUP test code 3001581

Dilated Cardiomyopathy Specimen	Whole Blood
Dilated Cardiomyopathy Interp	Positive

INDICATION FOR TESTING
Dilated cardiomyopathy

RESULT
One pathogenic variant was detected in the LMNA gene.

PATHOGENIC VARIANT
Gene: LMNA (NM_005572.3)
Nucleic Acid Change: c.1003C>T; Heterozygous
Amino Acid Alteration: p.Arg335Trp
Inheritance: Autosomal Dominant/Autosomal Recessive

INTERPRETATION
One pathogenic variant, c.1003C>T; p.Arg335Trp, was detected in the LMNA gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic variants in LMNA are associated with autosomal dominant dilated cardiomyopathy 1A (MIM: 115200), Emery-Dreifuss muscular dystrophy 2 (MIM: 181350), Slovenian type heart-hand syndrome (MIM: 610140), congenital muscular dystrophy (MIM: 613205), Malouf syndrome (MIM: 212112), and autosomal recessive Emery-Dreifuss muscular dystrophy 3 (MIM: 616516). This result is consistent with a diagnosis of dilated cardiomyopathy. This individuals offspring have a 50 percent chance of inheriting the pathogenic variant.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. 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 LMNA c.1003C>T; p.Arg335Trp variant (rs386134243) has been reported in multiple individuals with dilated cardiomyopathy or another LMNA-associated disorder (Lakdawala 2012, Pugh 2014, Sousa 2019, Walsh 2017, Zaragoza 2017). This variant has also been reported to co-segregate with disease in affected individuals of at least two families (Stallmeyere 2012, Zaragoza 2017). The p.Arg335Trp variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. The arginine at residue 335 is highly conserved, it occurs in the functionally important coil 2B domain (Bollati 2012), and computational algorithms (PolyPhen-2, SIFT) predict that the variant is deleterious. 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 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report, but are available upon request.

REFERENCES
Bollati M et al. Structures of the lamin A/C R335W and E347K mutants: implications for dilated cardiolaminopathies. Biochem Biophys Res Commun. 2012 Feb 10;418(2):217-21.

Lakdawala N et al. Genetic testing for dilated cardiomyopathy in clinical practice. J Card Fail. 2012; 18(4):296-303.

Pugh T et al. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. Genet Med. 2014; 16(8):601-8.

Sousa A et al. Molecular characterization of Portuguese patients with dilated cardiomyopathy. Rev Port Cardiol. 2019 Feb;38(2):129-139.

Stallmeyer B et al. Identification of novel mutations in LMNA associated with familial forms of dilated cardiomyopathy. Genet Test Mol Biomarkers. 2012; 16(6):543-9.

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

Zaragoza MV et al. Heart-hand syndrome IV: a second family with LMNA-related cardiomyopathy and brachydactyly. Clin Genet. 2017 Mar;91(3):499-500.

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	21-112-114930	4/22/2021 1:44:00 PM	4/22/2021 1:44:19 PM	4/22/2021 1:54:00 PM
Dilated Cardiomyopathy Interp	21-112-114930	4/22/2021 1:44:00 PM	4/22/2021 1:44:19 PM	4/22/2021 1:54:00 PM

END OF CHART

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