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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1752
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

LMNA-Related Disorders (LMNA) Sequencing

ARUP test code 2004543

LMNA Sequencing Specimen	Whole Blood
LMNA Sequencing Interpretation	**Positive** *

TEST PERFORMED - 2004543
TEST DESCRIPTION - LMNA-Related Disorders (LMNA) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the LMNA gene.

DNA VARIANT
Classification: Pathogenic
Gene: LMNA
Nucleic Acid Change: c.673C>T; Heterozygous
Amino Acid Alteration: p.Arg225Ter

INTERPRETATION
One pathogenic variant, c.673C>T; p.Arg225Ter, was detected in the LMNA gene by bidirectional sequencing. This result is consistent with a diagnosis of an LMNA-related disorder. This individual's offspring have a 50% chance of inheriting the pathogenic variant.

Evidence for variant classification: The LMNA c.673C>T; p.Arg225Ter variant (rs60682848) is reported in the literature in multiple individuals and co-segregates with disease in multiple families affected with laminopathy phenotypes, including dilated cardiomyopathy, cardiac conduction disease, and sudden cardiac death (Arimura 2013, Carboni 2012, Jakobs 2001, Laksman 2014, Mellor 2017, Parks 2008, Saga 2009, Siu 2012, van Tintelen 2007, Walsh 2017). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 48074), and is absent from general population databases (1000 Genomes Project, Exome Variant Server, and Genome Aggregation Database), indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Indeed, functional analyses of the variant protein show haploinsufficiency associated with apoptosis under electrical stimulation (Siu 2012). Based on available information, the p.Arg225Ter variant is considered to be pathogenic.

RECOMMENDATIONS
A medical genetics consultation, including a discussion of medical screening and management, is indicated. At-risk family members should be offered targeted testing for the identified

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

LMNA variant (Familial Mutation, Targeted Sequencing, ARUP test 2001961).

COMMENTS
Reference Sequence: GenBank # NM_170707.2 (LMNA)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not included in this report.

REFERENCES
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Mellor G et al. Genetic Testing in the Evaluation of Unexplained Cardiac Arrest: From the CASPER (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry). Circ Cardiovasc Genet. 2017 Jun;10(3). pii: e001686.
Parks SB et al. Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. Am Heart J. 2008 Jul;156(1):161-9.
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Siu CW et al. Modeling of lamin A/C mutation premature cardiac aging using patient-specific induced pluripotent stem cells. Aging (Albany NY). 2012 Nov;4(11):803-822.
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This result has been reviewed and approved by [redacted]

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BACKGROUND INFORMATION: LMNA-Related Disorders (LMNA) Sequencing
CHARACTERISTICS OF LAMINOPATHIES: Mutations in the lamin A/C (LMNA) gene cause a broad range of clinical diseases collectively termed laminopathies. Clinical findings are highly variable.
Hutchinson-Gilford progeria syndrome (HGPS): Accelerated aging, profound failure to thrive, characteristic facies, alopecia, joint degeneration, growth retardation. Average life span is 13 years.
Emery-Dreifuss muscular dystrophy, type 2 (EDMD2): Joint contractures, progressive muscle weakness and wasting, and cardiac disease with conduction defects and arrhythmias.
Familial partial lipodystrophy, Dunnigan type (FLPD): Post-pubescent progressive loss of subcutaneous fat from the extremities and excess fat accumulation on the face and neck.
Mandibuloacral dysplasia (MAD): Post-natal growth retardation, craniofacial and skeletal anomalies, mottled cutaneous pigmentation.
Atypical Werner syndrome (WS): Progeria-like syndrome with features of partial alopecia, premature aging, short stature, hypogonadism, osteoporosis, premature atherosclerosis, weak voice, cataracts.
Restrictive Dermopathy (RD): Skin tightness causes fetal akinesia or hypokinesia deformation sequence; disease is lethal.
INCIDENCE: At least 1 in 8 million for HGPS; DCM occurs in approximately 1 in 2,500 and is familial in 30-60 percent of cases of which approximately 8 percent are caused by LMNA gene mutations; unknown for other LMNA-related conditions.
INHERITANCE: Laminopathies are inherited as autosomal dominant, recessive, or de novo.
PENETRANCE: Complete for HGPS; variable for other LMNA-related disorders.
Cause: Pathogenic LMNA gene mutations.
Clinical Sensitivity: Clinical sensitivity is dependant upon the specific LMNA-related disorder.
METHODOLOGY: Bidirectional sequencing of the LMNA coding region and intron-exon boundaries.
Analytical Sensitivity and Specificity: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Some regulatory region mutations, deep intronic mutations, and large deletion/duplications will not be detected.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
LMNA Sequencing Specimen	19-336-112304	12/2/2019 1:08:00 PM	12/2/2019 1:14:19 PM	12/4/2019 8:51 00 AM
LMNA Sequencing Interpretation	19-336-112304	12/2/2019 1:08:00 PM	12/2/2019 1:14:19 PM	12/4/2019 8:51 00 AM

END OF CHART

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