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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Emery-Dreifuss Muscular Dystrophy Panel, Sequencing

ARUP test code 3001839

Emery-Dreifuss Muscular Dystrophy Spec	Whole Blood
Emery-Dreifuss Muscular Dystrophy Interp	Positive

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

RESULT
One pathogenic variant was detected in the EMD gene.

PATHOGENIC VARIANT
Gene: EMD (NM_000492.3)
Nucleic Acid Change:c.187+1G>A; Hemizygous
Inheritance: X-linked

INTERPRETATION
One pathogenic variant, c.187+1G>A, was detected in the EMD gene by massively parallel sequencing. Pathogenic variants in EMD are associated with X-linked Emery-Dreifuss muscular dystrophy 1 (MIM: 310300). This result is consistent with a diagnosis of Emery-Dreifuss muscular dystrophy. All of this individual's daughters will be carriers, but none of the sons will inherit 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 EMD c.187+1G>A variant is reported in the literature in multiple patients affected with Emery-Dreifuss muscular dystrophy (Deymeer 1993, Yates 1999, Steckiewicz 2016). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant disrupts the canonical splice donor site of intron 2, which is likely to negatively impact gene function. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic EMD variant (Familial Targeted Sequencing, ARUP test code 3005867).

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
Deymeer F et al. Emery-Dreifuss muscular dystrophy with unusual features. Muscle Nerve. 1993 Dec;16(12):1359-65. PMID: 8232393

Yates JR et al. Genotype-phenotype analysis in X-linked Emery-Dreifuss muscular dystrophy and identification of a missense mutation associated with a milder phenotype Neuromuscul Disord. 1999 May;9(3):159-65. PMID: 10382909

Steckiewicz R et al. Cardiac pacing in 21 patients with Emery-Dreifuss muscular dystrophy: a single-centre study with a 39-year follow-up. Kardiol Pol. 2016;74(6):576-83. PMID: 26575312

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Emery-Dreifuss Muscular Dystrophy Panel, Sequencing

CHARACTERISTICS: Emery-Dreifuss muscular dystrophy (EDMD) is characterized by a clinical triad of early onset joint contractures (commonly involving elbows, ankles, and neck), slowly progressive limb muscle weakness and wasting, and cardiac disease. EDMD demonstrates intra- and interfamilial variability in age of onset, severity, and progression; although penetrance is high. Typical presentation includes joint contractures in first two decades of life, followed by muscle weakness and wasting, with cardiac involvement occurring in the second to third decades. Carrier females of X-linked EDMD are usually asymptomatic, but are at risk for developing cardiac disease, and less commonly, mild muscle disease.

EPIDEMIOLOGY: Prevalence 1-2:100,000.

CAUSE: Pathogenic germline variants in EMD, FHL1, or LMNA.

INHERITANCE: X-linked for EMD or FHL1. Typically, autosomal dominant for LMNA; de novo variation is common. Autosomal recessive inheritance for LMNA is rare.

CLINICAL SENSITIVITY: 36 percent for EDMD.

GENES TESTED: EMD, FHL1, LMNA.

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 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.

LIMITATIONS: A negative result does not exclude a diagnosis of EDMD. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. In males, lack of massively parallel sequencing coverage of one or more EMD or FHL1 exons may suggest the presence of large deletions; however, this should be confirmed by a validated method. 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. Noncoding transcripts were not analyzed.

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
Emery-Dreifuss Muscular Dystrophy Spec	22-301-104538	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Emery-Dreifuss Muscular Dystrophy Interp	22-301-104538	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