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

Physician: Doctor, Example

Patient: Patient, Example

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

Duchenne/Becker Muscular Dystrophy (DMD) Sequencing

ARUP test code 2011153

DMD Sequencing Specimen	Whole Blood
DMD Sequencing Interpretation	Positive

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

RESULT
One pathogenic variant was detected in the DMD gene.

PATHOGENIC VARIANT
Gene: DMD (NM_004006.2)
Nucleic Acid Change: c.9851G>A; Hemizygous
Amino Acid Alteration: p.Trp3284Ter
Inheritance: X-linked

INTERPRETATION
One pathogenic variant, c.9851G>A; p.Trp3284Ter, was detected in the DMD gene by massively parallel sequencing. Variants in DMD are causative for Duchenne/Becker muscular dystrophy (MIM: 310200 / 300376); therefore, this individual is predicted to be affected. Female offspring will be carriers of the disease and may be variably affected; male offspring will be neither carriers of nor affected with the disease.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The DMD c.9851G>A; p.Trp3284Ter variant (rs398124104) is reported in the literature in several individuals affected with Duchenne muscular dystrophy or dilated cardiomyopathy (Gigli 2019, Nishiyama 2008, Takeshima 2010). This variant is reported in ClinVar (Variation ID: 322632) and is absent from the 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. Additionally, several downstream truncating variants have been described in affected individuals (Flanigan 2009, Takeshima 2010). Based on available information, this variant is classified as 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 DMD 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
Flanigan K et al. Mutational spectrum of DMD mutations in dystrophinopathy patients: application of modern diagnostic techniques to a large cohort. Hum Mutat. 2009 Dec;30(12):1657-66. PMID: 19937601.

Gigli M et al. Genetic Risk of Arrhythmic Phenotypes in Patients With Dilated Cardiomyopathy. J Am Coll Cardiol. 2019 Sep 17;74(11):1480-1490. PMID: 31514951.

Nishiyama A et al. Dystrophin nonsense mutations can generate alternative rescue transcripts in lymphocytes. Ann Hum Genet. 2008 Nov;72(Pt 6):717-24. PMID: 18652600.

Takeshima Y et al. Mutation spectrum of the dystrophin gene in 442 Duchenne/Becker muscular dystrophy cases from one Japanese referral center. J Hum Genet. 2010 Jun;55(6):379-88. PMID: 20485447.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Duchenne/Becker Muscular Dystrophy (DMD) Sequencing

CHARACTERISTICS: Symptoms of Duchenne muscular dystrophy (DMD) usually begin in childhood and include fatigue, learning difficulties, muscle weakness, progressive difficulty walking with eventual wheelchair dependency, breathing difficulties and heart disease. Symptoms of Becker muscular dystrophy (BMD) are similar to DMD but begin at a later age and progress at a slower rate. Dilated cardiomyopathy has been observed in nearly all affected males and many female carriers of DMD and BMD.

EPIDEMIOLOGY: Incidence of DMD: 1 in 3,500 male births, BMD: 1 in 19,000 male births.

INHERITANCE: X-linked; de novo variants occur in 1/3 of cases.

PENETRANCE: Males: 100 percent. Females: Varies with X-chromosome inactivation.

CLINICAL SENSITIVITY: DMD 20-35 percent. BMD: 10-20 percent.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the DMD gene, 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: 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 muscular dystrophy. This test only detects variants within the coding regions and intron-exon boundaries of the DMD gene. Regulatory region variants 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 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.

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
DMD Sequencing Specimen	22-301-101347	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
DMD Sequencing Interpretation	22-301-101347	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