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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/6/1998
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Duchenne/Becker Muscular Dystrophy (DMD) Deletion/Duplication with Reflex to Sequencing

ARUP test code 2011241

Duchenne/Becker MD (DMD) Reflex Specimen	Whole Blood
Duchenne/Becker MD (DMD) DelDup MLPA	**Duplication** *
Duchenne/Becker MD (DMD) Reflex Interp	See Note

TEST PERFORMED 2011241
TEST DESCRIPTION - Duchenne/Becker Muscular Dystrophy (DMD) Deletion/Duplication with Reflex to Sequencing
INDICATION FOR TESTING - Carrier Status. Previously identified DMD duplication. Manifesting carrier of Duchenne/Becker muscular dystrophy.
RESULT
One likely pathogenic variant was detected in the DMD gene.

DNA VARIANT
Classification: Likely Pathogenic
Gene: DMD
Nucleic Acid Change: Duplication of exon(s) 03-04; Heterozygous In-frame duplication

INTERPRETATION
According to information provided to ARUP, this individual is a manifesting carrier of Duchenne/Becker muscular dystrophy due to a duplication in DMD that was identified by previous genetic testing. The patient's mother is also reported to have had genetic testing which revealed a duplication.

The likely pathogenic familial duplication, which we identified as involving exon(s) 03-04, was detected by deletion/duplication analysis. This duplication is not expected to alter the reading frame. This variant was reported to be associated with Duchenne/Becker muscular dystrophy in the family; therefore, this individual is predicted to be at least a carrier and may be variably affected. Although females are usually asymptomatic, approximately 5-20 percent of carrier females may develop symptoms including variable degrees of muscle weakness and/or cardiomyopathy. This individuals male offspring have a 50 percent chance of being affected with disease while female offspring have a 50 percent chance of being a carrier and variably affected.

A pathogenic variant was detected by deletion/duplication analysis, therefore, DMD sequencing was not performed.

Evidence for variant classification: Duplication of exons 3-4 in DMD is reported in multiple individuals affected with

Duchenne/Becker muscular dystrophy (Barseghyan 2017, del Gaudio 2008, Ishizaki 2015, Nallamilli 2021, Piluso 2011). If found in tandem, this duplication event is expected to result in an in-frame product; however, this assay does not determine breakpoint positions, so it is uncertain whether all or part of the identified exons are duplicated. Based on available information, the duplication of exons 3-4 is considered likely 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 variant (Duchenne/Becker Muscular Dystrophy (DMD) Deletion/Duplication; ARUP test code 2011235).

COMMENTS
Reference Sequence: GenBank # NM_004006.2

Note: A positive familial control was not tested.

REFERENCES
American Academy of Pediatrics Section on Cardiology and Cardiac Surgery. Cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy. Pediatrics. 2005; 116(6):1569-73.

Barseghyan H et al. Next-generation mapping: a novel approach for detection of pathogenic structural variants with a potential utility in clinical diagnosis. Genome Med. 2017 Oct 25;9(1):90. PMID: 29070057.

del Gaudio et al. Molecular diagnosis of Duchenne/Becker muscular dystrophy: enhanced detection of dystrophin gene rearrangements by oligonucleotide array-comparative genomic hybridization. Hum Mutat. 2008 Sep;29(9):1100-7. PMID: 18752307.

Ishizaki M et al. Life-threatening Arrhythmias in a Becker Muscular Dystrophy Family due to the Duplication of Exons 3-4 of the Dystrophin Gene. Intern Med. 2015;54(23):3075-8. PMID: 26631896.

Nallamilli BRR et al. A single NGS-based assay covering the entire genomic sequence of the DMD gene facilitates diagnostic and newborn screening confirmatory testing. Hum Mutat. 2021 May;42(5):626-638. PMID: 33644936.

Piluso G et al. Motor chip: a comparative genomic hybridization microarray for copy-number mutations in 245 neuromuscular disorders. Clin Chem. 2011 Nov;57(11):1584-96. PMID: 21896784.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Duchenne/Becker Muscular Dystrophy (DMD) Deletion/Duplication with Reflex to 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 is 1 in 3,500 male births; Incidence of BMD is 1 in 19,000 male births.

INHERITANCE: X-linked; de novo variants occur in one-third of cases.

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

CLINICAL SENSITIVITY: Approximately 95 percent.

METHODOLOGY: Multiplex ligation-dependent probe amplification (MLPA) of the DMD gene. If results were negative or inconclusive, testing was reflexed to 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 for MLPA is greater than 99 percent. The analytical sensitivity for sequencing 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 by sequencing, 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 and breakpoints of large deletions/duplications will not be determined. 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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Duchenne/Becker MD (DMD) Reflex Specimen	23-230-402038	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Duchenne/Becker MD (DMD) DelDup MLPA	23-230-402038	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Duchenne/Becker MD (DMD) Reflex Interp	23-230-402038	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