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

Glycogen Storage Disorders Panel, Sequencing

ARUP test code 3001627

Glycogen Storage Disease Specimen	Whole Blood

GSD NGS Interp: Positive

RESULT
Two apparent copies of a pathogenic variant were detected in the GAA gene.

PATHOGENIC VARIANT
Gene: GAA (NM_000152.5)
Nucleic Acid Change: c.2560C>T; Homozygous
Amino Acid Alteration: p.Arg854Ter
Inheritance: Autosomal recessive

INTERPRETATION
Two apparent copies of a pathogenic variant, c.2560C>T; p.Arg854Ter, were detected in the GAA gene by massively parallel sequencing. Pathogenic variants in GAA are associated with autosomal recessive glycogen storage disease II (MIM: 232300). This result is consistent with a diagnosis of glycogen storage disease; clinical manifestations are variable. This individual's offspring have a 50 percent chance of inheriting 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 GAA c.2560C>T; p.Arg854Ter variant (rs121907943) is reported in the literature as homozygous and as compound heterozygous in numerous individuals affected with glycogen storage disease type II (Becker 1998, McCready 2007, Messinger 2012, Reuser 2019). Additionally, this variant is the most common variant reported in individuals with infantile onset Pompe disease (Reuser 2019), especially in those of African descent. This variant is reported in ClinVar and is classified as pathogenic by an expert panel (Variation ID: 4034). This variant is found in the African population with an allele frequency of 0.2% (47/24858 alleles) in the Genome Aggregation Database. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic and dietary consultations are recommended, including a discussion of medical screening and management. At-risk family members should be offered testing for the the identified

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

pathogenic GAA variant (Familial Targeted Sequencing, ARUP test code 3005867). This individual's reproductive partner should be offered GAA genetic testing to determine carrier status.

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
Becker JA et al. The African origin of the common mutation in African American patients with glycogen-storage disease type II. Am J Hum Genet. 1998 Apr;62(4):991-4. PMID: 9529346.
McCready ME et al. Development of a clinical assay for detection of GAA mutations and characterization of the GAA mutation spectrum in a Canadian cohort of individuals with glycogen storage disease, type II. Mol Genet Metab. 2007 Dec;92(4):325-35. PMID: 17723315.
Messinger YH et al. Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease. Genet Med. 2012 Jan;14(1):135-42. PMID: 22237443.
Reuser AJJ et al. GAA variants and phenotypes among 1,079 patients with Pompe disease: Data from the Pompe Registry. Hum Mutat. 2019 Nov;40(11):2146-2164. PMID: 31342611.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Glycogen Storage Disorders Panel, Sequencing

CHARACTERISTICS: Glycogen storage diseases (GSD) are a group of inborn errors of metabolism, typically caused by enzyme defects, resulting in a buildup of glycogen in the liver, muscles, and other organs. Common clinical features of these disorders include hepatomegaly, hypoglycemia, slow growth, cardiomyopathy, and muscle weakness. Other disorders with a similar clinical presentation to GSD are included on this panel.

EPIDEMIOLOGY: Incidence of GSD ranges from 1 in 10,000 to 1 in one million, depending on specific types and ethnic backgrounds.

CAUSE: Pathogenic germline variants in the GYS1, G6PC, SLC37A4, GAA, AGL, GBE1, PYGM, PYGL, PFKM, PHKA2, PHKB, PHKG2, PHKA1, PGAM2, SLC2A2, ALDOA, ENO3, and GYG1 genes are associated with glycogen storage diseases.
Pathogenic germline variants in the ACAT1, ALDOB, CPT2, FBP1, GYS2, LAMP2, LDHA, NHLRC1, OXCT1, PGK1, PGM1, PRKAG2, RBCK1, and SLC16A1 genes are associated with disorders that have phenotypes similar to GSD.

INHERITANCE: Autosomal recessive; X-linked recessive for PHKA1 and PHKA2 genes.

PENETRANCE: Variable

CLINICAL SENSITIVITY: Variable, depending on GSD type and subtype.

GENES TESTED: ACAT1, AGL, ALDOA, ALDOB, CPT2, ENO3*, FBP1, G6PC, GAA, GBE1, GYG1, GYS1, GYS2, LAMP2, LDHA, NHLRC1, OXCT1*, PFKM*, PGAM2, PGK1, PGM1, PHKA1, PHKA2, PHKB, PHKG2, PRKAG2, PYGL, PYGM, RBCK1, SLC16A1, SLC2A2, SLC37A4

*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 confirm reported variants.

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 glycogen storage disorder. 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, including GBE1 (NM_000158.4) intron 15. Deletions/duplications/insertions of any size may not be detected by massively 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. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
ENO3(NM_001374524) exon(s) 1
OXCT1(NM_001364299) exon(s) 5
OXCT1(NM_001364300) exon(s) 1
OXCT1(NM_001364303) exon(s) 1
PFKM(NM_001354735) exon(s) 4
PFKM(NM_001354736) exon(s) 4
PFKM(NM_001354740) exon(s) 1
PFKM(NM_001354741) exon(s) 2
The following may not be detected:
An Ashkenazi Jewish founder mutation in GBE1 (HGMD ID: CX153579)

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.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Glycogen Storage Disease Specimen	22-301-104962	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
GSD NGS Interp	22-301-104962	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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