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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/20/1949
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Gaucher Disease (GBA) Sequencing

ARUP test code 3001648

GBA FGS- Specimen	Whole Blood
GBA FGS Interpretation	Positive

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

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

DNA VARIANT
Classification: Pathogenic
Gene: GBA
Nucleic Acid Change: c.1226A>G; Homozygous
Amino Acid Alteration: p.Asn409Ser

INTERPRETATION
Two apparent copies of a pathogenic variant, c.1226A>G; p.Asn409Ser, were detected in the GBA gene by sequencing. This individual is predicted to be affected with Gaucher disease. Symptoms and age of onset are highly variable. Because sequence analysis is unable to detect large deletions, this individual either has two copies of the identified variant or a single copy of the variant and a deletion on the opposite chromosome. Parental testing could determine which of the above scenarios is correct for the purposes of testing other family members.

Evidence for variant classification: The GBA c.1226A>G; p.Asn409Ser variant (rs76763715), also known as N370S, is a common pathogenic variant reported in the homozygous and compound heterozygous state in individuals with type I Gaucher disease (Fairley 2008, Grace 1994, Tsuji 1988). While this variant is found in the Ashkenazi Jewish population with an overall allele frequency of 2.7% (279/10368 alleles) in the Genome Aggregation Database, it is commonly associated with disease in individuals of Ashkenazi Jewish descent (Tsuji 1988). The asparagine at codon 409 is moderately conserved, and functional studies demonstrate this variant has reduced enzymatic activity (Grace 1994, Tsuji 1988). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Parental testing is recommended to confirm whether they have the identified GBA variant or a large GBA deletion. Family members should be offered testing for the variant identified in their family lineage. Carrier screening for Gaucher disease should be offered to this individual's reproductive partner.

COMMENTS
Reference Sequence: GenBank # NM_001005741.2 (GBA)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
Fairley C et al. Phenotypic heterogeneity of N370S homozygotes with type I Gaucher disease: an analysis of 798 patients from the ICGG Gaucher Registry. J Inherit Metab Dis. 2008;31(6):738-744. PMID: 18979180.
Grace ME et al. Analysis of human acid beta-glucosidase by site-directed mutagenesis and heterologous expression. J Biol Chem. 1994;269(3):2283-2291. PMID: 8294487.
Tsuji S et al. Genetic heterogeneity in type 1 Gaucher disease: multiple genotypes in Ashkenazic and non-Ashkenazic individuals. Proc Natl Acad Sci U S A. 1988;85(7):2349-2352. PMID: 3353383.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Gaucher Disease (GBA) Sequencing

CHARACTERISTICS: Gaucher disease (GD) is a lysosomal storage disorder with phenotypes ranging from perinatal lethality to lack of symptoms. There are three GD subtypes. Type 1 GD manifests with bone disease, hepatosplenomegaly, anemia, thrombocytopenia, and lung disease but no central nervous system (CNS) involvement. Type 2 GD exhibits CNS symptoms before age 2 and rapidly progresses resulting in death by age 4. Type 3 GD presents as early as age 2 with CNS symptoms that slowly progress resulting in death during the third or fourth decade.
INCIDENCE: 1 in 900 Ashkenazi Jewish individuals; approximately 1 in 57,000 to 1 in 75,000 in general population.
INHERITENCE: Autosomal recessive.
CAUSE: Two pathogenic GBA variants on opposite chromosomes.
CLINICAL SENSITIVITY: 99 percent.
METHODOLOGY: Long range PCR followed by bidirectional sequencing of all coding regions and intron-exon boundaries of the GBA gene.
ANALYTICAL SENSITIVITY AND SPECIFICITY: approximately 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region variants, deep intronic variants, large deletions/duplications/insertions, gene conversion and complex gene events may not be detected.

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
GBA FGS- Specimen	24-017-109838	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
GBA FGS Interpretation	24-017-109838	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