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

Connexin 26 (GJB2) Sequencing and Deletion/Duplication

ARUP test code 3004720

CX26 Specimen	Whole Blood
CX26 Interp	Positive

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

RESULT
Two copies of a pathogenic variant were detected in the GJB2 gene.

PATHOGENIC VARIANT
Gene: GJB2 (NM_004004.6)
Nucleic Acid Change: c.35delG; Homozygous
Amino Acid Alteration: p.Gly12ValfsTer2
Inheritance: Autosomal recessive

INTERPRETATION
Two copies of a pathogenic variant, c.35delG; p.Gly12ValfsTer2, were detected in the GJB2 (Connexin 26) gene by massively parallel sequencing. Pathogenic variants in GJB2 are commonly associated with autosomal recessive deafness-1A (DFNB1A, MIM: 220290). This individual is predicted to have autosomal recessive nonsyndromic hearing loss.

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

Evidence for variant classification:
The GJB2 c.35delG; p.Gly12ValfsTer2 variant (rs80338939) is the most common pathogenic GJB2 variant found among individuals with European ancestry (Estivill 1998, Gasparini 2000). It has been described in the homozygous and compound heterozygous state in individuals affected with autosomal recessive nonsyndromic hearing loss with severity ranging from mild to profound (Estivill 1998, Gasparini 2000, Putcha 2007). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 17004) and is observed in the general population at an overall frequency of 0.6% (1737/280696 alleles, 10 homozygotes) in the Genome Aggregation Database. This variant causes a frameshift by deleting a single nucleotide, and in vitro functional studies demonstrate a loss of connexin 26 function (D'Andrea 2002). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Medical management should rely on clinical findings and family history. Family members should be offered targeted testing for the identified pathogenic variant (Familial Targeted Sequencing, ARUP test code 3005867). This individual's reproductive partner should be offered screening for GJB2 and GJB6 pathogenic variants.

COMMENTS
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
D'Andrea P et al. Hearing loss: frequency and functional studies of the most common connexin26 alleles. Biochem Biophys Res Commun. 2002 Aug 23;296(3):685-91. PMID: 12176036
Estivill X et al. Connexin-26 mutations in sporadic and inherited sensorineural deafness. Lancet. 1998 Feb 7;351(9100):394-8. PMID: 9482292
Gasparini P et al. High carrier frequency of the 35delG deafness mutation in European populations. Genetic Analysis Consortium of GJB2 35delG. Eur J Hum Genet. 2000 Jan;8(1):19-23. PMID: 10713883
Putcha G et al. A multicenter study of the frequency and distribution of GJB2 and GJB6 mutations in a large North American cohort. Genet Med. 2007 Jul;9(7):413-26. PMID: 17666888

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Connexin 26 (GJB2) Sequencing and Deletion/Duplication

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

CHARACTERISTICS: Biallelic autosomal recessive GJB2 variants are associated with autosomal recessive deafness type 1A (DFNB1A), characterized by mild to profound nonsyndromic hearing loss (NSHL) that is typically nonprogressive. A pathogenic GJB2 variant on the opposite chromosome from a large GJB6 gene deletion, involving GJB2 cis-regulatory elements and loss of expression of GJB2, is also causative for NSHL. Autosomal dominant GJB2 sequence variants are causative for a variety of phenotypes including autosomal dominant deafness type 3A (DFNA3A) and syndromic forms of hearing loss which may include keratosis or ichthyosis.

EPIDEMIOLOGY: Approximately 1:6500

CAUSE: Pathogenic germline variants in GJB2

INHERITANCE: Autosomal recessive or dominant depending on specific GJB2 variant

CLINICAL SENSITIVITY: Greater than 99 percent for GJB2-associated hearing loss (DFNB1A)

GENE TESTED: GJB2 (NM_004004).

METHODOLOGY: Probe hybridization-based capture of all coding exons, exon-intron junctions, and selected noncoding variants of the GJB2 gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the GJB2 gene. Large deletions/duplications were confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions and duplications of the full GJB2 coding exon are detected with 97 percent and 83 percent sensitivity, respectively. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a heritable form of hearing loss. This test only detects variants within the coding regions, intron-exon boundaries, and selected noncoding variants of the GJB2 gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. 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 U.S. 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
CX26 Specimen	22-301-101302	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
CX26 Interp	22-301-101302	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