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

Physician: Doctor, Example

Patient: Patient, Example

DOB	1/14/1990
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Alport Syndrome Panel, Sequencing and Deletion/Duplication

ARUP test code 3002685

Alport Syndrome Specimen	Whole Blood

Alport Syndrome Interp

Positive

RESULT
One likely pathogenic variant was detected in the COL4A5 gene.

LIKELY PATHOGENIC VARIANT
Gene: COL4A5 (NM_000495.5)
Nucleic Acid Change: c.4874_4877del; Hemizygous
Amino Acid Alteration: p.Arg1625GlnfsTer27
Inheritance: X-linked

INTERPRETATION
One likely pathogenic variant, c.4874_4877del; p.Arg1625GlnfsTer27, was detected in the COL4A5 gene by massively parallel sequencing. Pathogenic COL4A5 variants are inherited in an X-linked recessive manner and are associated with Alport syndrome. This result is consistent with a diagnosis of Alport syndrome. All of his daughters will be carriers, but none of his sons will inherit 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 COL4A5 c.4874_4877del; p.Arg1625GlnfsTer27 variant, to our knowledge, is not reported in the medical literature or gene specific databases. This variant is also absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant causes a frameshift by deleting four nucleotides, so it 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 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 likely pathogenic COL4A5 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:

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

NONE

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Alport Syndrome Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Alport syndrome (AS) is characterized by a triad of renal insufficiency, sensorineural hearing loss (SNHL), and ocular findings. The disease spectrum ranges from a slowly progressive disorder with renal insufficiency and SNHL late in life to SNHL in the first decade of life and end-stage renal disease (ESRD) by age 20. Individuals with MYH9-related disease have enlarged platelets and thrombocytopenia; some will also have adult-onset renal disease and SNHL, but cataracts are uncommon.

PREVALENCE of AS: 1 in 50,000 births

CAUSE: Pathogenic germline variants in COL4A3, COL4A4, and COL4A5 are causative for AS. Pathogenic MYH9 gene variants are causative for MYH9-related disease.

INHERITANCE: X-linked for COL4A5, autosomal dominant and autosomal recessive for COL4A3 and COL4A4, and autosomal dominant for MYH9.

PENETRANCE: Complete for males with pathogenic COL4A5 variants and individuals with two pathogenic COL4A3 or COL4A4 variants on opposite chromosomes. May be incomplete for autosomal dominant COL4A3 and COL4A4 variants. Complete for MYH9-related disease.

CLINICAL SENSITIVITY: Approaching 100 percent for AS; at least 98 percent for MYH9-related disease

GENES TESTED: COL4A3; COL4A4; COL4A5; MYH9.

METHODOLOGY: Probe hybridization-based 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 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 indicated genes. Large deletions/duplications 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 of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of AS or MYH9-related disease. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. 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. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be

identified. Single exon deletions are reported but called at a lower sensitivity. 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) mutations, 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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Alport Syndrome Specimen	23-253-400038	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Alport Syndrome Interp	23-253-400038	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