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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1752
Sex:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Cystic Fibrosis (CFTR) Sequencing and Deletion/Duplication

ARUP test code 3004745

CFTR Specimen	Whole Blood
CFTR Interp	Positive

RESULT
Two pathogenic variants were detected in the CFTR gene.

PATHOGENIC VARIANT
Gene: CFTR (NM_000492.4)
Nucleic Acid Change: c.1521_1523delCTT; heterozygous
Amino Acid Alteration: p.Phe508del
Inheritance: Autosomal recessive

PATHOGENIC VARIANT
Gene: CFTR (NM_000492.4)
Nucleic Acid Change: c.489+2T>G; heterozygous
Inheritance: Autosomal recessive

INTERPRETATION
One copy of a pathogenic variant, c.1521_1523delCTT; p.Phe508del, was detected by Sanger sequencing, and one copy of a pathogenic variant, c.489+2T>G, was detected by massively parallel sequencing in the CFTR gene. If the variants are located on opposite chromosomes, this molecular result is consistent with a diagnosis of cystic fibrosis (CF); however, disease severity, including pancreatic sufficiency, may be variable.

No additional pathogenic variants were identified in the CFTR gene by sequencing or deletion/duplication analysis. Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

Evidence for variant classifications: The CFTR p.Phe508del (F508del) variant is the most common pathogenic CFTR variant that has been reported in Whites (Sosnay, 2013; CFTR2 database). This variant is considered to cause cystic fibrosis when identified with another pathogenic variant on the opposite chromosome.

The CFTR c.489+2T>G variant (rs397508732), also known as 621+2T>G, is reported in the literature in individuals affected with cystic fibrosis (Claustres, 1993; des Georges, 2004; see link to cystic fibrosis mutation database). This variant is also reported in ClinVar (Variation ID: 53970) but is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant disrupts the canonical splice donor site of intron 4, which is likely to negatively impact gene function. Additionally, another variant at this nucleotide

(c.489+2T>C) has been reported in individuals with cystic fibrosis and is considered pathogenic (Malone, 1998). Based on available information, the c.489+2T>G variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation and referral to a CF clinic for disease management is indicated. Targeted sequencing for both identified variants is recommended for this individual's parents and symptomatic siblings (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Other adult family members should be offered carrier testing for the variant identified in their family lineage. Carrier screening is recommended for this individuals reproductive partner (Cystic Fibrosis 165 Pathogenic Variants, ARUP test code 2013661).

COMMENTS
Likely benign and benign variants are not reported.

REFERENCES
Claustres M, et al. Analysis of the 27 exons and flanking regions of the cystic fibrosis gene: 40 different mutations account for 91.2% of the mutant alleles in southern France. Hum Mol Genet. 1993;2(8):1209-1213. PMID: 7691344.

des Georges M, et al. High heterogeneity of CFTR mutations and unexpected low incidence of cystic fibrosis in the Mediterranean France. J Cyst Fibros. 2004;3(4):265-272. PMID: 15698946.

Link to CFTR2 database: http://cftr2.org/

Link to cystic fibrosis mutation database for c.489+2T>G: http://www.genet.sickkids.on.ca/cftr/MutationDetailPage.external?sp=114

Malone G, et al. Detection of five novel mutations of the cystic fibrosis transmembrane regulator (CFTR) gene in Pakistani patients with cystic fibrosis: Y569D, Q98X, 296+12(T>C), 1161delC and 621+2(T>C). Hum Mutat. 1998;11(2):152-7. PMID: 9482579.

Sosnay P et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet. 2013;45(10):1160-1167. PMID: 23974870.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Cystic Fibrosis (CFTR) Sequencing and Deletion/Duplication

CHARACTERISTICS: Cystic fibrosis (CF) and CFTR-related disorders are caused by biallelic pathogenic variants in the CFTR gene. Age of onset, manifestations, and symptom severity vary greatly. Symptoms of classic CF include chronic sinopulmonary disease, pancreatic insufficiency, hepatic disease, prolapsed rectum, meconium ileus, obstructive azoospermia, and salt loss syndromes. CFTR-related disorders are less severe and may be characterized by isolated pancreatitis, bilateral absence of the vas deferens, chronic bronchiectasis, and/or nasal polyposis.

EPIDEMIOLOGY: CF is more common in individuals of Ashkenazi Jewish and Caucasian/White descent (approximately 1 in 2,300 and 1 in 2,500 individuals, respectively). CF is less common in individuals of Hispanic, African American/Black, and Asian American descent (approximately 1 in 13,500, 1 in 15,100, and 1 in 35,100, respectfully).

CAUSE: Biallelic pathogenic variants in the CFTR gene

INHERITANCE: Autosomal recessive

CLINICAL SENSITIVITY: 99 percent

GENE TESTED: CFTR (NM_000492)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the CFTR gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage or known low quality, 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 CFTR gene. 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 two exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of three 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 CF. This test only detects variants within the coding regions and intron-exon boundaries of the CFTR 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. 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 two 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
CFTR Specimen	22-136-101245	5/16/2022 8:47 00 AM	5/16/2022 8:47:19 AM	5/16/2022 9:04:00 AM
CFTR Interp	22-136-101245	5/16/2022 8:47 00 AM	5/16/2022 8:47:19 AM	5/16/2022 9:04:00 AM

END OF CHART