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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/5/1987
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Cystic Fibrosis (CFTR) Sequencing (Temporary Referral as of 12/07/20)

ARUP test code 0051110

CF CFTR Specimen	Whole Blood
Cystic Fibrosis (CFTR) Sequencing	Positive

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TEST PERFORMED - 0051110
TEST DESCRIPTION - Cystic Fibrosis (CFTR) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant and one pathogenic variant of varying
clinical consequences were detected in the CFTR gene.

DNA VARIANTS
Classification: Pathogenic
Gene: CFTR
Nucleic Acid Change: c.1521_1523delCTT  Heterozygous
Amino Acid Alteration: p.Phe508del

Classification: Pathogenic - Varying Clinical Consequences
Gene: CFTR
Nucleic Acid Change: c.3454G>C; Heterozygous
Amino Acid Alteration: p.Asp1152His

INTERPRETATION
One copy of a pathogenic variant, c.1521_1523delCTT;
p.Phe508del, and one copy of a pathogenic variant of varying
clinical consequences, c.3454G>C; p.Asp1152His, were detected in
the CFTR gene by sequencing. If these variants occur on opposite
chromosomes, this molecular result may cause cystic fibrosis
(CF), a CFTR-related disorder (pancreatitis, lung disease, or
bilateral absence of the vas deferens), or no symptoms. Because
of this variability, clinical criteria alone should be used to
determine whether this individual has CF (CFTR2 database).

Evidence for variant classifications: The CFTR p.Phe508del
(F508del) variant is the most common pathogenic CFTR variant
that has been reported in Caucasians (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.3454G>C; p.Asp1152His variant (rs75541969) is
reported in the literature in multiple individuals affected with
classic cystic fibrosis or CFTR-related disorders (Chillon 1995,
Gallati 2009, Highsmith 2005, LaRusch 2014, Masson 2013, Steiner
2011, Sosnay 2013, CFTR2 database). This variant is reported as
pathogenic by multiple laboratories in ClinVar (Variation ID:
35867) and is found in the general population with an overall
allele frequency of 0.038% (104/276606 alleles) in the Genome
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H=High, L=Low, *=Abnormal, C=Critical

Aggregation Database. The aspartic acid at codon 1152 is moderately conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. Functional characterization of the variant protein indicates a significant reduction in chloride and bicarbonate transport activity (LaRusch 2014, Sosnay 2013, Van Goor 2014, Vankeerberghen 1998). Genotype-phenotype correlation studies have demonstrated that this variant, in combination with another pathogenic CFTR variant (e.g., p.Phe508del), is associated with highly variable clinical presentations, ranging from asymptomatic to pancreatic insufficient CF (Burgel 2010, Mussaffi 2006, Terlizzi 2015, CFTR2 database). Based on available information, the p.Asp1152His variant is classified as pathogenic with variable presentation of clinical phenotypes.

RECOMMENDATIONS
Medical management should rely on clinical findings and family history. Genetic consultation 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 testing for the variant identified in their family lineage. This individual's reproductive partner should be offered carrier screening (Cystic Fibrosis 165 Pathogenic Variants, ARUP test code 2013661).

COMMENTS
Reference Sequence: GenBank # NM_000492.3 (CFTR)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
CFTR2 database: http://cftr2.org/

Burgel P et al. Non-classic cystic fibrosis associated with D1152H CFTR mutation. Clin Genet. 2010; 77(4):355-64.

Chillon M et al. Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. N Engl J Med. 1995; 332(22):1475-80.

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Highsmith WE Jr et al. A CFTR mutation (D1152H) in a family with mild lung disease and normal sweat chlorides. Clin Genet. 2005; 68(1):88-90.

LaRusch J et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. PLoS Genet. 2014; 10(7):e1004376.

Masson E et al. A conservative assessment of the major genetic causes of idiopathic chronic pancreatitis: data from a comprehensive analysis of PRSS1, SPINK1, CTRC and CFTR genes in 253 young French patients. PLoS One. 2013; 8(8):e73522.

Mussaffi H et al. Cystic fibrosis mutations with widely variable phenotype: the D1152H example. Pediatr Pulmonol. 2006; 41(3):250-4.

Sosnay PR et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet. 2013; 45(10):1160-7.

Steiner B et al. Common CFTR haplotypes and susceptibility to chronic pancreatitis and congenital bilateral absence of the vas deferens. Hum Mutat. 2011; 32(8):912-20.

Terlizzi V et al. Clinical expression of patients with the D1152H CFTR mutation. J Cyst Fibros. 2015; 14(4):447-52.

Van Goor F et al. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. J Cyst Fibros. 2014; 13(1):29-36.

Vankeerberghen A et al. Characterization of 19 disease-associated missense mutations in the regulatory domain of the cystic fibrosis transmembrane conductance regulator. Hum Mol Genet. 1998; 7(11):1761-9.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Cystic Fibrosis (CFTR) Sequencing

CHARACTERISTICS: Chronic sino-pulmonary disease, gastrointestinal malabsorption/pancreatic insufficiency, and obstructive azoospermia. Findings are often limited to a single organ system such as isolated pancreatitis, bilateral absence of the vas deferens, nasal polyposis, or bronchiectasis in non-classic cystic fibrosis (CF).
INCIDENCE OF CLASSIC CF: 1 in 3,000 Caucasians or Ashkenazi Jewish, 1 in 8,000 Hispanics, 1 in 15,000 African Americans, 1 in 32,000 Asians.
INCIDENCE OF NONCLASSIC CF: Unknown.
INHERITANCE: Autosomal recessive.
PENETRANCE: High for severe mutations, variable for mild/moderate mutations.
CAUSE OF CLASSIC CF: Two deleterious CFTR mutations on opposite chromosomes.
CAUSE OF NONCLASSIC CF: Typically one severe and one mild/moderate CFTR mutations on opposite chromosomes.
CLINICAL SENSITIVITY: 97 percent.
METHODOLOGY: Bidirectional sequencing of the entire CFTR coding region, intron-exon boundaries, and two deep intronic mutations.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations, large gene deletions/duplications and some deep intronic mutations will not be detected.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
CF CFTR Specimen	20-300-400015	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cystic Fibrosis (CFTR) Sequencing	20-300-400015	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