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

Physician: Doctor, Example

Patient: Patient, Example

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

Familial Mutation, Targeted Sequencing, Fetal

ARUP test code 2001980

SEQ FSM FE Specimen	Amniotic fluid
Targeted Sequencing Gene	CFTR
Targeted Sequencing Interpretation	**Positive** *

TEST PERFORMED - 2001980
TEST DESCRIPTION - Familial Mutation, Targeted Sequencing, Fetal
INDICATION FOR TEST - Predictive Testing

RESULT
The fetus is positive for both requested variants in the CFTR gene.

DNA VARIANTS
Pathogenic-Severe
CFTR
Nucleic Acid Change: c.1521_1523delCTT Heterozygous
Amino Acid Alteration: p.Phe508del (F508del)

Varying Clinical Consequences
CFTR
Nucleic Acid Change: c.3454G>C; Heterozygous
Amino Acid Alteration: p.Asp1152His (D1152H)

INTERPRETATION
The fetus inherited both familial CFTR gene variants, the maternal c.1521_1523delCTT; p.Phe508del (F508del) variant and the paternal c.3454G>C; p.Asp1152His (D1152H) variant, based upon targeted sequencing.

The F508del variant is the most common pathogenic CFTR variant that has been reported in Caucasians (Sosnay 2013, CFTR2 database) and is considered a severe pathogenic variant. The D1152H variant has been reported in individuals with classic cystic fibrosis (CF) or CFTR-related disorders (Chillon 1995, Highsmith 2005, Gallati 2009, Steiner 2011, Masson 2013, LaRusch 2014, CFTR2 database). Genotype-phenotype correlation studies have demonstrated that this variant, in combination with another pathogenic CFTR variant (e.g., F508del), is associated with variable clinical presentations, ranging from asymptomatic to pancreatic insufficient CF (Mussaffi 2006, Burgel 2010, Terlizzi 2015, CFTR2 database). Because of this, the D1152H variant is characterized as having variable expression or penetrance.

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

Because of the phenotypic variability associated with D1152H, it is not possible to predict the consequences of inheriting both familial variants. Although this fetus may be at risk for developing a CFTR-related disorder, clinical criteria alone should be used to determine whether or not an individual with a variant of varying clinical consequences has CF (CFTR2 database).

RECOMMENDATIONS
Genetic consultation is recommended. For quality assurance purposes, ARUP Laboratories will confirm the above result at no charge following delivery. Order Confirmation of Fetal Testing and include a copy of the original fetal report (or the mother's name and date of birth) with the test submission. Please contact an ARUP genetic counselor (800-242-2787 ext 2141) prior to specimen submission.

COMMENTS
Reference Sequence: GenBank # NM_000492.3 (CFTR)
Nucleotide numbering begins at the "A" of the ATG initiation codon.

Note: A positive familial control was tested.

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

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

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

Gallati S et al (2009) Cystic fibrosis transmembrane conductance regulator mutations in azoospermic and oligospermic men and their partners. Reprod Biomed Online. 19(5):685-94.

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

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

Masson E et al. (2013) 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. 8(8):e73522.

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

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

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

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

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

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Cystic Fibrosis (CFTR) Targeted Sequencing

CHARACTERISTICS: Classic cystic fibrosis (CF) is characterized by chronic sino-pulmonary disease, gastrointestinal malabsorption/pancreatic insufficiency and obstructive azoospermia; clinical findings in atypical CF are often limited to a single organ system.
INCIDENCE: 1 in 3000 Caucasians or Ashkenazi Jewish, 1 in 8000 Hispanics, 1 in 15,000 African Americans, 1 in 32,000 Asians.
INHERITANCE: Autosomal recessive.
Penetrance: High for two severe mutations, variable for mild mutations.
CAUSE: Classic CF results from two severe or moderate CFTR gene mutations on different chromosomes; atypical CF is often caused by two mild mutations, one mutation and one variant or a severe mutation and a variant.
METHODOLOGY: PCR followed by bidirectional sequencing of the specific CFTR mutation(s) requested.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Rare diagnostic errors can occur due to primer site mutations. Mutations in the CFTR gene, other than the one(s) specifically requested, were not evaluated.

BACKGROUND INFORMATION: Familial Mutation, Targeted Sequencing

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

Maternal Contamination Study Fetal Spec	Fetal Cells

Single fetal genotype present; no maternal cells present. Fetal and maternal samples were tested using STR markers to rule out maternal cell contamination.

INTERPRETIVE INFORMATION: Maternal Cell Contamination, Fetal Specimen
Please refer to fetal report for interpretation.

Maternal Contam Study, Maternal Spec	Whole Blood

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
SEQ FSM FE Specimen	17-011-118818	1/11/2017 6:38 00 PM	1/11/2017 6:39:13 PM	1/18/2017 5:57:00 PM
Targeted Sequencing Gene	17-011-118818	1/11/2017 6:38 00 PM	1/11/2017 6:39:13 PM	1/18/2017 5:57:00 PM
Targeted Sequencing Interpretation	17-011-118818	1/11/2017 6:38 00 PM	1/11/2017 6:39:13 PM	1/18/2017 5:57:00 PM
Maternal Contamination Study Fetal Spec	17-011-118818	1/11/2017 6:38 00 PM	1/11/2017 6:39:13 PM	1/18/2017 5:57:00 PM
Maternal Contam Study, Maternal Spec	17-011-118818	1/11/2017 6:38 00 PM	1/11/2017 6:39:13 PM	1/18/2017 5:57:00 PM

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