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

Physician: Doctor, Example

Patient: Patient, Example

DOB	8/8/2019
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Citrullinemia, Type I (ASS1) Sequencing

ARUP test code 2007069

Citrullinemia, Type I (ASS1)Seq Specimen	Whole Blood

Citrullinemia, Type I (ASS1) Seq Interp: See Note *

```
TEST PERFORMED - 2007069
TEST DESCRIPTION - Citrullinemia, Type I (ASS1) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the ASS1 gene.

DNA VARIANT
Classification: Pathogenic
Gene: ASS1
Nucleic Acid Change: c.1087C>T; Heterozygous
Amino Acid Alteration: p.Arg363Trp

INTERPRETATION
One copy of the pathogenic variant, c.1087C>T; p.Arg363Trp, was
detected in the ASS1 gene by sequencing. This individual is at
least a carrier of citrullinemia type I (CTLN1) and may be
affected if a second, undetected pathogenic variant is present
on the opposite chromosome. Please refer to the background
information included in this report for the clinical sensitivity
and limitations of this test.

Evidence for variant classification: The ASS1 c.1087C>T;
p.Arg363Trp variant (rs121908640) is reported in the literature
in multiple individuals affected with citrullinemia, either in a
homozygous state or compound heterozygous with another
pathogenic variant (Diez-Fernandez 2017, Faghfoury 2011  Gao
2003, Haberle 2003, Kobayashi 1990, Mohamed 2015, Wasant 2005).
This variant is reported as pathogenic or likely pathogenic by
multiple laboratories in ClinVar (Variation ID: 6328), and is
only observed on 8 alleles in the Genome Aggregation Database,
indicating it is not a common polymorphism. The arginine at
codon 363 is moderately conserved, and computational analyses
(SIFT: damaging, PolyPhen-2: benign) predict conflicting effects
of this variant on protein structure/function. However, arginine
363 is implicated in tetramer binding, which is critical for
protein function (Diez-Fernandez 2017). Additionally, other
amino acid substitutions at this codon (Gly, Leu, Gln) have been
reported in individuals with citrullinemia (Gao 2003, Mohamed
2015). Based on available information, the p.Arg363Trp variant
is considered to be pathogenic.

RECOMMENDATIONS
Medical and dietary management should rely on clinical and
```

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

biochemical findings. If clinical suspicion for citrullinemia type I remains high, consideration should be given to ASS1 deletion/duplication analysis (not available at ARUP). Genetic consultation is recommended.

Family members, ideally beginning with the parents, should be offered testing for the pathogenic variant (Familial Mutation, Targeted Sequencing; ARUP test code 2001961). This individual's future reproductive partner should be offered ASS1 genetic testing to determine carrier status.

COMMENTS
Reference Sequence: GenBank # NM_000050.4 (ASS1)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
Diez-Fernandez C et al. Mutations in the Human Argininosuccinate Synthetase (ASS1) Gene, Impact on Patients, Common Changes, and Structural Considerations. Hum Mutat. 2017 May;38(5):471-484.

Faghfoury H et al. Transient fulminant liver failure as an initial presentation in citrullinemia type I. Mol Genet Metab. 2011; 102(4):413-7.

Gao H et al. Identification of 16 novel mutations in the argininosuccinate synthetase gene and genotype-phenotype correlation in 38 classical citrullinemia patients. Hum Mutat. 2003; 22(1):24-34.

Haberle J et al. Mild citrullinemia in Caucasians is an allelic variant of argininosuccinate synthetase deficiency (citrullinemia type 1). Mol Genet Metab. 2003 Nov;80(3):302-6.

Kobayashi K et al. Heterogeneity of mutations in argininosuccinate synthetase causing human citrullinemia. J Biol Chem. 1990; 265(19):11361-7.

Mohamed S et al. Neurometabolic Disorders-Related Early Childhood Epilepsy: A Single-Center Experience in Saudi Arabia. Pediatr Neonatol. 2015 Dec;56(6):393-401.

Wasant P et al. Argininosuccinate synthetase deficiency: mutation analysis in 3 Thai patients. Southeast Asian J Trop Med Public Health. 2005; 36(3):757-61.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Citrullinemia, Type I (ASS1) Sequencing:

Characteristics: Classic citrullinemia type I is a urea cycle disorder characterized by hyperammonemia, lethargy, vomiting, coma and neonatal death if not treated. There is also a milder, late-onset form and a form in which women have onset of severe symptoms during pregnancy or postpartum.
Incidence: Approximately 1 in 57,000.
Inheritance: Autosomal recessive.
Penetrance: Variable.
Cause: Pathogenic ASS1 gene mutations.
Clinical Sensitivity: Approximately 96 percent.
Methodology: Bidirectional sequencing of the entire ASS1 coding region and intron/exon boundaries.
Analytical Sensitivity and Specificity: 99 percent.
Limitations: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations, deep intronic mutations, and large deletions/duplications will not be detected. Mutations in genes other than ASS1 are not evaluated.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Citrullinemia, Type I (ASS1)Seq Specimen	19-269-134740	9/26/2019 3:15:00 PM	9/28/2019 4:10:00 PM	10/4/2019 4:26:00 PM
Citrullinemia, Type I (ASS1) Seq Interp	19-269-134740	9/26/2019 3:15:00 PM	9/28/2019 4:10:00 PM	10/4/2019 4:26:00 PM

END OF CHART