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

Physician: Doctor, Example

Patient: Patient, Example

DOB	4/9/1946
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Familial Transthyretin Amyloidosis (TTR) Sequencing

ARUP test code 3004531

TTR Specimen	Whole Blood
TTR Interp	Positive

RESULT
One pathogenic variant was detected in the TTR gene.

PATHOGENIC VARIANT
Gene: TTR (NM_000371.4)
Nucleic Acid Change: c.148G>A; Heterozygous
Amino Acid Alteration: p.Val50Met
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.148G>A; p.Val50Met, was detected in the TTR gene by massively parallel sequencing. Pathogenic TTR variants are inherited in an autosomal dominant manner and are associated with familial transthyretin amyloidosis (MIM: 105210). This result is consistent with a diagnosis of familial transthyretin amyloidosis; clinical manifestations are variable. This individual's offspring have a 50 percent chance to inherit the pathogenic variant and would be at-risk for developing the clinical features associated with familial transthyretin amyloidosis.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The TTR c.148G>A; p.Val50Met variant (rs28933979), also known as Val30Met, is the most common pathogenic TTR variant associated with familial amyloidotic polyneuropathy worldwide (Parman 2016). The variant has a variable clinical presentation ranging from asymptomatic carriers to systemic disease, having early-late onset disease subtypes (Arvidsson 2015, Beirao 2015, Coelho 2017, Parman 2016). Functional studies suggest the variant refolds from monomers to tetramers at a slower rate compared to wildtype (Jesus 2016), has decreased stability in the folded state (Altland 2007), and impairs the inflammatory response necessary for nerve regeneration (Goncalves 2014). This variant is reported as pathogenic in ClinVar (Variation ID: 13417), and observed in the general population with an overall allele frequency of 0.01% (25/246236 alleles) in the Genome Aggregation Database. Computational analyses predict that this variant is deleterious (REVEL: 0.711). Additionally, other variants at this codon (p.Val50Ala, p.Val50Leu) have been reported in individuals with amyloid neuropathy and are considered pathogenic (Altland 2007, Suhr 2009). Based on available information, the p.Val50Met variant is considered to

be pathogenic.

RECOMMENDATIONS
Genetic consultation, including a discussion of medical screening and management, is indicated. At-risk family members should be offered testing for the identified pathogenic TTR variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
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:
NONE

REFERENCES
Altland K et al. Genetic microheterogeneity of human transthyretin detected by IEF. Electrophoresis. 2007 Jun;28(12):2053-64. PMID: 17503405.
Arvidsson S et al. Amyloid Cardiomyopathy in Hereditary Transthyretin V30M Amyloidosis - Impact of Sex and Amyloid Fibril Composition. PLoS One. 2015 Nov 23;10(11):e0143456. PMID: 26600306.
Beirao JM et al. Ophthalmological manifestations in hereditary transthyretin (ATTR V30M) carriers: a review of 513 cases. Amyloid. 2015;22(2):117-22. PMID: 26096568.
Coelho T et al. Clinical measures in transthyretin familial amyloid polyneuropathy. Muscle Nerve. 2017 Mar;55(3):323-332. PMID: 27422379.
Goncalves NP et al. The inflammatory response to sciatic nerve injury in a familial amyloidotic polyneuropathy mouse model. Exp Neurol. 2014 Jul;257:76-87. PMID: 24800914.
Jesus CS et al. A New Folding Kinetic Mechanism for Human Transthyretin and the Influence of the Amyloidogenic V30M Mutation. Int J Mol Sci. 2016 Aug 31;17(9). PMID: 27589730.
Parman Y et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol. 2016 Feb;29 Suppl 1:S3-S13. PMID: 26734951.
Suhr OB et al. Report of five rare or previously unknown amyloidogenic transthyretin mutations disclosed in Sweden. Amyloid. 2009 Dec;16(4):208-14. PMID: 19922332.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Familial Transthyretin Amyloidosis (TTR) Sequencing

CHARACTERISTICS: Familial transthyretin amyloidosis (ATTR) is caused by pathogenic variants of the TTR gene resulting in abnormal amyloid accumulation in various tissues and is generally categorized into three phenotypes: 1) familial amyloid polyneuropathy, a slowly progressive sensorimotor and autonomic neuropathy; 2) familial amyloid cardiomyopathy, a restrictive cardiomyopathy with cardiomegaly, conduction block, angina, congestive heart failure, and aortic dissection/dilatation; and 3) leptomeningeal amyloidosis, primarily affecting the central nervous systems, causing dementia, visual impairment, seizures, ataxia, psychosis, hemorrhage, and hydrocephalus. TTR variants can also be associated with benign familial euthyroid hyperthyroxinemia.

EPIDEMIOLOGY: 1 in 538 individuals from northern Portugal; 1 in 100,000 individuals of northern European descent in the U.S.

CAUSE: Pathogenic germline TTR variants.

INHERITANCE: Autosomal dominant.

PENETRANCE: Incomplete.

CLINICAL SENSITIVITY: 99 percent for familial TTR amyloidosis.

GENE TESTED: TTR (NM_000371)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the TTR gene, 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. 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. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of hereditary amyloidosis. This test only detects variants within the coding regions and intron-exon boundaries of the TTR gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants, deep intronic variants, and large deletions/duplications will not be identified. 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) variants, 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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
TTR Specimen	23-262-123742	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
TTR Interp	23-262-123742	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