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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/19/1977
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Early-Onset Alzheimer's Panel, Sequencing

ARUP test code 3001585

Alzheimer's Specimen	Whole Blood

Alzheimer's Interp	Positive

RESULT
One pathogenic variant was detected in the PSEN1 gene.

PATHOGENIC VARIANT
Gene: PSEN1 (NM_000021.4)
Nucleic Acid Change: c.1292C>A; Heterozygous
Amino Acid Alteration: p.Ala431Glu
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1292C>A; p.Ala431Glu, was detected in the PSEN1 gene by massively parallel sequencing. Pathogenic variants in PSEN1 are associated with autosomal dominant Alzheimer's disease type 3 (MIM: 607822). This result is consistent with a diagnosis of Alzheimer's disease. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The PSEN1 c.1292C>A; p.Ala431Glu (rs63750083) variant is reported in the literature in several individuals and families with Alzheimer's disease (Parker 2019, Portelius 2010, Soosman 2016) and is implicated as a founder variant in individuals from Jalisco state in Mexico (Murrell 2006). The variant is reported in the ClinVar database as pathogenic by several sources (Variation ID: 18155) but is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. The alanine at codon 431 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.946). Functional studies indicate this variant inhibits gamma secretase activity and impair its function as a calcium leak channel (Nelson 2010, Sun 2017). Based on available information, this variant is classified as pathogenic.

RECOMMENDATIONS
Genetic and neurological consultations are indicated, including a discussion of medical screening and management. Testing for the identified pathogenic PSEN1 variant should be made available to at-risk adult family members (Familial Targeted Sequencing, ARUP test code 3005867).

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

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.
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
Murrell J et al. The A431E mutation in PSEN1 causing familial Alzheimer's disease originating in Jalisco State, Mexico: an additional fifteen families. Neurogenetics. 2006 Nov;7(4):277-9. PMID: 16897084.
Nelson O et al. Familial Alzheimer's disease mutations in presenilins: effects on endoplasmic reticulum calcium homeostasis and correlation with clinical phenotypes. J Alzheimers Dis. 2010;21(3):781-93. PMID: 20634584.
Parker J et al. Homozygosity for the A431E mutation in PSEN1 presenting with a relatively aggressive phenotype. Neurosci Lett. 2019 Apr 23;699:195-198. PMID: 30716424.
Portelius E et al. Distinct cerebrospinal fluid amyloid beta peptide signatures in sporadic and PSEN1 A431E-associated familial Alzheimer's disease. Mol Neurodegener. 2010 Jan 14;5:2. PMID: 20145736.
Soosman SK et al. Widespread white matter and conduction defects in PSEN1-related spastic paraparesis. Neurobiol Aging. 2016 Nov;47:201-209. PMID: 27614114.
Sun L et al. Analysis of 138 pathogenic mutations in presenilin-1 on the in vitro production of AB42 and AB40 peptides by gamma-secretase. Proc Natl Acad Sci U S A. 2017 Jan 24;114(4):E476-E485. PMID: 27930341.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Early-Onset Alzheimer's Panel, Sequencing
CHARACTERISTICS: Alzheimer's disease (AD) is characterized by progressive memory loss leading to dementia. Up to 25 percent of AD may be hereditary. Less than 2 percent is the early-onset familial form defined as a diagnosis of AD before age 65, while 15-25 percent is a late-onset familial form. Although symptoms of familial early-onset AD are similar to late-onset (sporadic AD), there is a greatly increased chance of identifying a genetic etiology with early-onset AD. Diagnosis of AD requires autopsy or a molecular genetic confirmation.
EPIDEMIOLOGY: Nearly 6 million individuals in the U. S. are affected with AD; approximately 200,000 are <65 yrs.
CAUSE: Pathogenic germline APP, PSEN1 and PSEN2 gene variants are causative of early-onset AD.
INHERITANCE: Autosomal dominant.
PENETRANCE: PSEN2 has reduced penetrance.
CLINICAL SENSITIVITY: 60-80 percent for familial early-onset AD.
GENES TESTED: APP*, PSEN1, PSEN2
*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.
ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of sequencing is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.
LIMITATIONS: A negative result does not exclude a heritable form of early onset AD. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

The following region is not sequenced due to technical limitations of the assay:
APP (NM_001136016.3) exon 1

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Alzheimer's Specimen	23-293-400798	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Alzheimer's Interp	23-293-400798	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