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

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/28/2020
Sex:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (ACADVL) Sequencing and Deletion/Duplication

ARUP test code 3004419

VLCAD Specimen	Whole Blood
VLCAD Interp	Positive

RESULT
Two pathogenic variants were detected in the ACADVL gene.

PATHOGENIC VARIANT
Gene: ACADVL (NM_000018.4)
Nucleic Acid Change: c.956C>A; Heterozygous
Amino Acid Alteration: p.Ser319Ter
Inheritance: Autosomal Recessive

PATHOGENIC VARIANT
Gene: ACADVL (NM_000018.4)
Nucleic Acid Change: c.1405C>T; Heterozygous
Amino Acid Alteration: p.Arg469Trp
Inheritance: Autosomal Recessive

INTERPRETATION
Two pathogenic variants, c.956C>A; p.Ser319Ter, and c.1405C>T; p.Arg469Trp, were detected in the ACADVL gene by massively parallel sequencing. This individual is predicted to be affected with very long-chain acyl CoA (VLCAD) deficiency; clinical manifestations are highly variable. Although the identified variants have not previously been reported to occur on the same chromosome, parental testing could confirm they are located on opposite chromosomes.

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

Evidence for variant classifications:
The ACADVL c.956C>A p.Ser319Ter variant (rs149467828, ClinVar Variation ID: 557676) is reported in the literature in at least one individual affected with very long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency (Pena 2016). This variant is only observed on one allele in the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Additionally, several downstream truncating variants have been described in individuals with VLCAD deficiency and are considered pathogenic (Pena 2016). Based on available information, this variant is considered to be pathogenic.

The ACADVL c.1405C>T; p.Arg469Trp variant (rs113994170), also

known as Arg429Trp, has been reported in multiple individuals with VLCAD deficiency, including three severely affected individuals that were homozygous for the variant (Andresen 1999). Additionally, functional studies have shown that the variant protein has significantly reduced enzymatic activity (Goetzman 2007, Hoffmann 2012). This variant is reported in ClinVar (Variation ID: 21017) and is only observed on seven alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. The arginine at codon 469 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL:0.947). This variant resides at a CpG di-nucleotide of ACADVL that is defined as a mutational hotspot (Andersen 1999). Additionally, other variants at this codon c.1406G>A; p.Arg469Gln have been reported in individuals with VLCAD deficiency and are considered pathogenic (Akar 2021, Andersen 1999). Taken together, this variant is considered pathogenic.

RECOMMENDATIONS
Genetic and dietary consultations are strongly recommended, including a discussion of medical screening and management. Parental testing may be considered to confirm the chromosomal origin of the identified variants. At-risk family members should be offered testing for the identified variants (Familial Targeted Sequencing, ARUP test code 3005867). This individual's future reproductive partner should be offered ACADVL genetic testing to determine carrier status.

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
Akar HT et al. Complicated peripartum course in a patient with very long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency. Neuromuscul Disord. 2021 Jun;31(6):566-569. PMID: 33965301.
Andresen BS et al. Clear correlation of genotype with disease phenotype in very-long-chain acyl-CoA dehydrogenase deficiency. Am J Hum Genet. 1999 Feb;64(2):479-94. PMID: 9973285
Goetzman ES et al. Expression and characterization of mutations in human very long-chain acyl-CoA dehydrogenase using a prokaryotic system. Mol Genet Metab. 2007 Jun;91(2):138-47. PMID: 17374501
Hoffmann L et al. VLCAD enzyme activity determinations in newborns identified by screening: a valuable tool for risk assessment. J Inherit Metab Dis. 2012 Mar;35(2):269-77. PMID: 21932095
Pena LD et al. Outcomes and genotype-phenotype correlations in 52 individuals with VLCAD deficiency diagnosed by NBS and enrolled in the IBEM-IS database. Mol Genet Metab. 2016 Aug;118(4):272-81. PMID: 27209629.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (ACADVL) Sequencing and Deletion/Duplication

CHARACTERISTICS: VLCAD deficiency is a long-chain fatty acid oxidation disorder associated with three phenotypes that vary in age of onset and severity. Clinical symptoms may include cardiomyopathy, pericardial effusion, hypotonia, hepatomegaly, hypoketotic hypoglycemia, skeletal myopathy, exercise intolerance, and rhabdomyolysis induced by exercise.

EPIDEMIOLOGY: Approximately 1 in 40,000

CAUSE: Pathogenic germline variants in the ACADVL gene

INHERITANCE: Autosomal recessive

CLINICAL SENSITIVITY: 95-97 percent

GENE TESTED: ACADVL (NM_000018)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the ACADVL gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications were confirmed using an orthogonal exon-level microarray. 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. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of VLCAD deficiency. This test only detects variants within the coding regions and intron-exon boundaries of the ACADVL gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. 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) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding 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 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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
VLCAD Specimen	25-072-114614	3/13/2025 11:25:00 AM	3/14/2025 2:08:24 PM	3/27/2025 9:30:00 AM
VLCAD Interp	25-072-114614	3/13/2025 11:25:00 AM	3/14/2025 2:08:24 PM	3/27/2025 9:30:00 AM

END OF CHART

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