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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Peroxisomal Disorder Panel, Sequencing

ARUP test code 3002700

Peroxisomal Disorders Specimen	Whole Blood
Peroxisomal Disorders Interp	Positive

RESULT
Two pathogenic variants were detected in the PEX1 gene.

PATHOGENIC VARIANT
Gene: PEX1 (NM_000466.3)
Nucleic Acid Change: c.781C>T; Heterozygous
Amino Acid Alteration: p.Gln261Ter
Inheritance: Autosomal recessive

PATHOGENIC VARIANT
Gene: PEX1 (NM_000466.3)
Nucleic Acid Change: c.2528G>A; Heterozygous
Amino Acid Alteration: p.Gly843Asp
Inheritance: Autosomal recessive

INTERPRETATION
Two pathogenic variants, c.781C>T; p.Gln261Ter, and c.2528G>A; p.Gly843Asp, were detected in the PEX1 gene by massively parallel sequencing. Pathogenic PEX1 variants are inherited in an autosomal recessive manner and are associated with Zellweger spectrum disorders (MIM: 234580, 214100, 601539). This molecular result is consistent with a clinical diagnosis of a Zellweger spectrum disorder if the two identified variants are present on opposite chromosomes; clinical manifestations are variable.

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 classifications:
The PEX1 c.781C>T; p.Gln261Ter variant (rs61750403) has been reported in the literature in individuals affected with peroxisome biogenesis disorders (Tamura 2001). This variant is also absent from the Genome Aggregation Database, 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. Based on available information, this variant is considered to be pathogenic.

The PEX1 c.2528G>A; p.Gly843Asp variant (rs61750420) is the most common PEX1 variant in patients with peroxisome biogenesis disorders (Ebberink 2011, Reuber 1997). This variant is also reported in ClinVar as pathogenic (Variation ID: 7516). This variant is found in the general population with an overall

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

allele frequency of 0.03% (89/282,722 alleles) in the Genome Aggregation Database. Functional cell-based studies of this variant demonstrate temperature-sensitive peroxisome assembly (Imamura 1998). The glycine at codon 843 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.98). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is recommended, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic PEX1 variants (Familial Targeted Sequencing, ARUP test code 3005867). This individual's reproductive partner should be offered genetic testing to determine carrier status.

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
Ebberink MS et al. Genetic classification and mutational spectrum of more than 600 patients with a Zellweger syndrome spectrum disorder. Human mutation. 2011 Jan. PMID: 21031596

Imamura A et al. Temperature-sensitive mutation in PEX1 moderates the phenotypes of peroxisome deficiency disorders. Hum Mol Genet. 1998 Dec. PMID: 9817926

Reuber BE et al. Mutations in PEX1 are the most common cause of peroxisome biogenesis disorders. Nature genetics. 1997 Dec. PMID: 9398847

Tamura S et al. Phenotype-genotype relationships in peroxisome biogenesis disorders of PEX1-defective complementation group 1 are defined by Pex1p-Pex6p interaction. Biochem J. 2001 Jul 15. PMID: 11439091

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Peroxisomal Disorders Panel, Sequencing

CHARACTERISTICS: Peroxisomal disorders are a group of diseases caused by gene defects impairing the formation (peroxisome biogenesis disorders) or function of the peroxisomes, with symptoms that impact a wide range of body systems. Peroxisome biogenesis disorders include Zellweger spectrum disorders (ZSD) and rhizomelic chondrodysplasia punctata (RCDP). Single enzyme defects include Refsum disease, peroxisomal acyl-CoA oxidase deficiency, peroxisomal bifunctional deficiency, defects of bile acid synthesis, and primary hyperoxaluria. Some single enzyme defects present with similar clinical features to ZSD (e.g. ACOX1, HSD17B4) or RCDP (e.g. AGPS, GNPAT), although these often can be distinguished by extensive biochemical testing. Signs and symptoms of peroxisomal disorders may develop as early as the newborn period, with hypotonia, seizures, poor growth, and feeding problems. Leukodystrophy, hepatic dysfunction, adrenal insufficiency, hearing loss, and visual impairment may also be present. Skeletal abnormalities in individuals with peroxisomal disorders include stippling of the growth plates and chondrodysplasia punctata, or progressive loss of bone mineral density. Later onset forms of these conditions have similar symptoms, but with a slower progression and milder severity. Developmental delay and intellectual disability are common.

INCIDENCE: Approximately 1 in 50,000

CAUSE: Pathogenic germline variants in genes associated with the structure and function of peroxisomes.

INHERITANCE: Autosomal recessive with rare autosomal dominant cases

CLINICAL SENSITIVITY: At least 97% for Zellweger spectrum disorders
At least 97% for rhizomelic chondrodysplasia punctata

GENES TESTED: ABCD3, ACBD5*, ACOX1, AGPS, AGXT, AMACR, DNM1L, FAR1, GNPAT, HSD17B4, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PHYH, SCP2*

* 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.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test 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 diagnosis of peroxisomal disorders. 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 massively 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 regions are not sequenced due to technical limitations of the assay:
ACBD5 (NM_001352568) exon(s) 6
ACBD5 (NM_001352569) exon(s) 6
ACBD5 (NM_001352570) exon(s) 13
ACBD5 (NM_001352571) exon(s) 5
ACBD5 (NM_001352573) exon(s) 6
ACBD5 (NM_001352574) exon(s) 6
ACBD5 (NM_001352575) exon(s) 6
ACBD5 (NM_001352576) exon(s) 6
ACBD5 (NM_001352581) exon(s) 6
ACBD5 (NM_001352585) exon(s) 5
ACBD5 (NM_001352586) exon(s) 5
ACBD5 (NM_001352568) partial exon(s) 1(Chr10:27529638-27529648)
ACBD5 (NM_001352572) partial exon(s) 1(Chr10:27529638-27529648)
SCP2 (NM_001007098) exon(s) 11
SCP2 (NM_001330587) exon(s) 12

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Peroxisomal Disorders Specimen	22-311-110826	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Peroxisomal Disorders Interp	22-311-110826	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