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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/5/2023
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication

ARUP test code 3002100

Tuberous Sclerosis Specimen	Whole Blood

Tuberous Sclerosis Interp

Positive

RESULT
One pathogenic variant was detected in the TSC1 gene.

PATHOGENIC VARIANT
Gene: TSC1 (NM_000368.5)
Nucleic Acid Change: c.2074del; Heterozygous
Amino Acid Alteration: p.Arg692GlufsTer32
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.2074del; p.Arg692GlufsTer32, was detected in the TSC1 gene by massively parallel sequencing. Pathogenic TSC1 variants are inherited in an autosomal dominant manner, and are associated with tuberous sclerosis complex (TSC). Therefore, this result is consistent with a diagnosis of TSC. Guidelines from the National Comprehensive Cancer Network (NCCN) and International Tuberous Sclerosis Consensus Conference are available for medical management in heterozygous individuals (NCCN Guidelines, Northrup 2021). This individual's future 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 TSC1 c.2074del; p.Arg692GlufsTer32 variant is reported in the literature in an individual with a central nervous system cancer (Kim 2021). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant causes a frameshift by deleting a single nucleotide, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Frameshift variants and other variants that introduce premature termination codons are responsible for the majority of TSC1 associated tuberous sclerosis (Curatolo 2015). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic TSC1 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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

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
Curatolo P et al. Genotype/Phenotype Correlations in Tuberous Sclerosis Complex. Semin Pediatr Neurol. 2015 Dec;22(4):259-73. PMID: 26706013.
Kim J et al. Frequency of Pathogenic Germline Variants in Cancer-Susceptibility Genes in the Childhood Cancer Survivor Study. JNCI Cancer Spectr. 2021 Jan 23;5(2):pkab007. PMID: 34308104.
National Comprehensive Cancer Network. Hereditary Renal Cell Carcinoma Guideline (3.2023): www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
Northrup H et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021 Oct;123:50-66. PMID: 34399110.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Tuberous sclerosis complex (TSC) is a multisystem, genetic disorder causing numerous benign tumors, as well as intellectual and developmental disabilities. Tumors can occur in the skin, brain, kidneys, and other organs, and can lead to significant health complications and may be life threatening.

PREVALENCE: 1 in 6,000 individuals

CAUSE: Pathogenic germline variants in TSC1 and TSC2

INHERITANCE: Autosomal dominant; approximately 66% are de novo

PENETRANCE: Complete penetrance with variable expressivity

CLINICAL SENSITIVITY: 95%

GENES TESTED: TSC1, TSC2

METHODOLOGY: Probe hybridization-based 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 to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications 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 TSC. This test only detects variants within the coding regions

and intron-exon boundaries of the targeted genes. 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. Noncoding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. The U.S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Tuberous Sclerosis Specimen	23-041-401684	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Tuberous Sclerosis Interp	23-041-401684	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