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

Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication, Fetal

ARUP test code 3002096

Maternal Contamination Study Fetal Spec	Fetal Cells Single fetal genotype present; no maternal cells present. Fetal and maternal samples were tested using STR markers to rule out maternal cell contamination.
Maternal Contam Study, Maternal Spec	Whole Blood For quality assurance purposes, ARUP Laboratories will confirm the above result at no charge following delivery. Order Confirmation of Fetal Testing and include a copy of the original fetal report (or the mother's name and date of birth) with the test submission. Please contact an ARUP genetic counselor at (800) 242-2787 extension 2141 prior to specimen submission.
Tuberous Sclerosis Fetal Specimen	Cultured Amnio
Tuberous Sclerosis Fetal Interp	Positive RESULT One pathogenic variant was detected in the TSC1 gene. PATHOGENIC VARIANT Gene: TSC1 (NM_000368.5) Nucleic Acid Change: c.2380C>T, Heterozygous Amino Acid Alteration: p.Gln794Ter Inheritance: Autosomal Dominant INTERPRETATION One pathogenic variant, c.2380C>T, p.Gln794Ter, was detected in the TSC1 gene by massively parallel sequencing in this prenatal sample. Pathogenic TSC1 variants are inherited in an autosomal dominant manner, and are associated with tuberous sclerosis complex (TSC). Therefore, this fetus is predicted to be affected. 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). 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:

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

The TSC1 c.2380C>T, p.Gln794Ter variant (rs781371665) is reported in the literature in several individuals with a diagnosis of tuberous sclerosis (Jiang 2021, Peron 2018, Pompili 2009). This variant is also reported in ClinVar (Variation ID: 489349), but is 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. Variants that introduce premature termination codons in TSC1 are responsible for almost all TSC1 associated tuberous sclerosis cases (Curatolo 2015). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated. At-risk family members should be offered testing for the identified pathogenic TSC1 variant (Familial Targeted Sequencing, ARUP test code 3005867). Because parental somatic or germline mosaicism for the identified TSC1 pathogenic variant cannot be excluded, the parents of this fetus should be offered prenatal diagnosis in future pregnancies.

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.
Jiang T et al. Application of Trio-Whole Exome Sequencing in Genetic Diagnosis and Therapy in Chinese Children With Epilepsy. Front Mol Neurosci. 2021 Aug 19;14:699574. PMID: 34489640.
National Comprehensive Cancer Network. Hereditary Renal Cell Carcinoma Guideline (4.2022): 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.
Peron A et al. Deep phenotyping of patients with Tuberous Sclerosis Complex and no mutation identified in TSC1 and TSC2. Eur J Med Genet. 2018 Jul;61(7):403-410. PMID: 29432982.
Pompili G et al. Magnetic resonance imaging of renal involvement in genetically studied patients with tuberous sclerosis complex. Eur J Radiol. 2009 Nov;72(2):335-41. PMID: 18835118.

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication, Fetal
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. 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.

BACKGROUND INFORMATION: Tuberous Sclerosis Complex Panel, Sequencing and Deletion/Duplication, Fetal
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CAUSE: Pathogenic germline variants in TSC1 and TSC2
INHERITANCE: Autosomal dominant; approximately 66 percent are de novo
PENETRANCE: Complete penetrance with variable expressivity
CLINICAL SENSITIVITY: 95 percent
GENES TESTED: TSC1, TSC2
METHODOLOGY: Targeted 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. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the targeted genes. Human genome build 19 (Hg 19) was used for data analysis.
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 TSC. 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 and breakpoints of large deletions / duplications will not be determined. Single exon deletions / duplications or deletions / duplications less than 1kb may not be detected. 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. Single exon deletions / duplications will not be called for the following exons: TSC2 (NM_000548) 17,29,41

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Maternal Contamination Study Fetal Spec	22-311-111149	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Maternal Contam Study, Maternal Spec	22-311-111149	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Tuberous Sclerosis Fetal Specimen	22-311-111149	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Tuberous Sclerosis Fetal Interp	22-311-111149	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