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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/9/1961
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Hereditary Hemorrhagic Telangiectasia (HHT) Panel, Sequencing and Deletion/Duplication

ARUP test code 2009337

HHT Panel Specimen	Whole Blood
HHT Panel Interpretation	Positive

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

INDICATION FOR TESTING
Nosebleeds and lung arteriovenous malformation (AVM).

RESULT
One pathogenic variant was detected in the ENG gene.

PATHOGENIC VARIANT
Gene: ENG (NM_001114753.2)
Nucleic Acid Change: c.771dupC; Heterozygous
Amino Acid Alteration: p.Tyr258fs
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.771dupC; p.Tyr258fs, was detected in the ENG gene by massively parallel sequencing and confirmed by Sanger sequencing. This result is consistent with a diagnosis of hereditary hemorrhagic telangiectasia (HHT) (MIM: 187300). Symptoms of HHT are highly variable, complex and age dependent. Variants in ENG are inherited in an autosomal dominant manner; therefore, this individual's offspring have a 50 percent chance of inheriting the causative variant.

No additional pathogenic variants were identified in the other targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The ENG c.771dupC; p.Tyr258fs variant has been previously reported in at least one patient affected with hereditary hemorrhagic telangiectasia (HHT) (Lesca 2004). This variant is absent from general population databases (1000 Genome Project, Exome Variant Server, and Genome Aggregation Database), indicating it is not a common polymorphism. This variant creates a frameshift by duplicating a single nucleotide, so it 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.

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 ENG variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Benign variants are not included in this report, but are available upon request.

REFERENCES
Lesca G et al. Molecular screening of ALK1/ACVRL1 and ENG genes in hereditary hemorrhagic telangiectasia in France. Hum Mutat. 2004 Apr;23(4):289-99.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Hereditary Hemorrhagic Telangiectasia (HHT) Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Telangiectases of the hands, mouth, face, and nasal and gastrointestinal mucosa. The most common symptom is recurrent nosebleeds. Arteriovenous malformations (AVMs), particularly of the lungs, liver, brain and spinal cord. Complications of internal organ AVMs include the effects of high flow shunting of blood (i.e. congestive heart failure secondary to liver AVMs or embolic stroke/brain abscess secondary to lung AVMs), as well as hemorrhage.

EPIDEMIOLOGY: The prevalence is 1 in 10,000.

CAUSE: Pathogenic germline variants in ENG, ACVLR1/ALK1 cause HHT. Pathogenic germline variants in SMAD4 are associated with juvenile polyposis syndrome and juvenile polyposis/HHT syndrome. Pathogenic germline variants in RASA1, EPHB4 and GDF2/BMP9 cause clinically overlapping disorders, also associated with cutaneous AVMs and/or telangiectases.

INHERITANCE: Autosomal dominant.

PENETRANCE: Greater than 90 percent by age 40, but age related and clinically variable.

CLINICAL SENSITIVITY: Approximately 87 percent for individuals who meet consensus clinical diagnostic criteria for HHT. Variable for those with symptoms but do not meet diagnostic criteria.

GENES TESTED: ACVRL1, ENG, EPHB4**, GDF2, RASA1, SMAD4

** - Deletion/duplication detection is not available for this gene.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. The 5' untranslated region of ENG and a region of ACVRL1 intron 9 encompassing the CT-rich variant hotspot region were also sequenced. 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 indicated subset of genes. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: 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 heritable form of hereditary hemorrhagic telangiectasia or overlapping 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 and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. In some circumstances, single exon insertions/deletions 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 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.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
HHT Panel Specimen	18-344-107339	12/10/2018 11:48:00 AM	12/10/2018 1:31:12 PM	12/10/2018 3:40:00 PM
HHT Panel Interpretation	18-344-107339	12/10/2018 11:48:00 AM	12/10/2018 1:31:12 PM	12/10/2018 3:40:00 PM

END OF CHART

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