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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/9/2003
Gender:	Male
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: Negative

INDICATION FOR TESTING
Patient referred for testing due to recurrent nosebleeds.

RESULT
No pathogenic variants were detected in any of the genes tested.

INTERPRETATION
No pathogenic variants were identified by massively parallel sequencing of the coding regions and exon-intron boundaries of the genes tested. No large exonic deletions and duplications were identified in the genes tested. This result decreases the likelihood of, but does not exclude, a diagnosis of hereditary hemorrhagic telangiectasia. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

RECOMMENDATIONS
Medical screening and management of this individual should rely on clinical findings and family history. Genetic consultation is recommended.

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

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

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

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	18-344-107390	12/10/2018 11:49:00 AM	12/10/2018 1:32:17 PM	12/10/2018 3:40:00 PM
HHT Panel Interpretation	18-344-107390	12/10/2018 11:49:00 AM	12/10/2018 1:32:17 PM	12/10/2018 3:40:00 PM

END OF CHART

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