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

Physician: Doctor, Example

Patient: Patient, Example

DOB	8/14/1975
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

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

ARUP test code 2009337

HHT Panel Specimen: Whole Blood

HHT Panel Interpretation: Positive

RESULT
One likely pathogenic variant was detected in the ACVRL1 gene.

LIKELY PATHOGENIC VARIANT
Gene: ACVRL1 (NM_000020.3)
Nucleic Acid Change: c.1133C>T; Heterozygous
Amino Acid Alteration: p.Pro378Leu
Inheritance: Autosomal dominant

INTERPRETATION
One likely pathogenic variant, c.1133C>T; p.Pro378Leu, was detected in the ACVRL1 gene by massively parallel sequencing. This result is consistent with a diagnosis of hereditary hemorrhagic telangiectasia (HHT; MIM: 600376). Symptoms of HHT are highly variable, complex and age dependent. Variants in ACVRL1 are inherited in an autosomal dominant manner; therefore, this individual's offspring have a 50 percent chance of inheriting the causative 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 ACVRL1 c.1133C>T; p.Pro378Leu variant is reported in the literature in an individual with HHT (Olivieri 2002). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. Computational analyses predict that this variant is deleterious (REVEL: 0.966). Additionally, other variants at this codon (p.Pro378Ser, p.Pro378Arg) are reported in individuals with HHT and considered causative (see ClinVar Variation IDs: 811496, 838395). Based on available information, the p.Pro378Leu variant is considered to be likely 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 likely pathogenic ACVRL1 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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

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

limitations:
NONE

REFERENCES
Olivieri C et al. Identification of 13 new mutations in the ACVRL1 gene in a group of 52 unselected Italian patients affected by hereditary haemorrhagic telangiectasia. J Med Genet. 2002 Jul;39(7):E39. PMID: 12114496.

This result has been reviewed and approved by Pinar Bayrak-Toydemir, M.D., Ph.D.
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 (e.g., congestive heart failure secondary to liver AVMs or embolic stroke/brain abscess secondary to lung AVMs), as well as hemorrhage.

EPIDEMIOLOGY: The prevalence is estimated to be 1 in 5,000 to 1 in 10,000 individuals.

CAUSE: Pathogenic germline variants in ACVLR1 and ENG cause HHT. Pathogenic germline variants in SMAD4 are associated with juvenile polyposis syndrome and juvenile polyposis/HHT syndrome. Pathogenic germline variants in BMPR2, EPHB4, GDF2/BMP9, and RASA1 cause clinically overlapping disorders, also associated with cutaneous AVMs and/or telangiectases.

INHERITANCE: Autosomal dominant for all genes tested

PENETRANCE: Approximately 95 percent by late adulthood for HHT

CLINICAL SENSITIVITY: Approximately 97 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, BMPR2, ENG*, EPHB4, GDF2, RASA1, SMAD4

*One or more exons are not covered by deletion/duplication analysis; see limitations section below.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, (including the 5' UTR of ENG, and a region of ACVRL1 intron 9 encompassing the CT-rich variant hotspot region), 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: 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 HHT or overlapping disorders. 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) variants, 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.

Single exon deletions/duplications may not be called in the following exons: ENG (NM_001114753, NM_000118) 1.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. 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.
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VERIFIED/REPORTED DATES				
Procedure	Accession	Collected	Received	Verified/Reported
HHT Panel Specimen	23-116-401608	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
HHT Panel Interpretation	23-116-401608	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

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