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HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Background: Hereditary Hemorrhagic Telangiectasia (HHT; OMIM 187300), also called Osler-Weber-Rendu disease, is a blood vessel disorder characterized by abnormal, direct connections between arteries and veins. Telangiectases, small abnormal blood vessels, which appear as red spots are often found on the lips, tongue, fingers, intestines, or nose. Larger abnormal blood vessels, called arteriovenous malformations (AVMs), can occur in the internal organs, most commonly the lung, liver, spine, and brain. Bleeding telangiectases in the nose or intestines can be either a minor annoyance or a major medical problem, sometimes requiring transfusions. Undetected and untreated lung, spine and brain AVMs can be a significant cause of life-threatening or disabling complications in individuals with HHT.

The majority of individuals with a clinical diagnosis of HHT will have an identifiable mutation in the *ENG* or *ACVRL1* genes. Additionally, about 2-3% of individuals with HHT but without juvenile polyposis were reportedly found to have a pathogenic variant in the SMAD4 gene.

Assay: Sequencing: Sanger sequencing of all coding exons and flanking intronic regions of *ENG*, *ACVRL1* and *SMAD4* genes.

Deletion/Duplication: A custom comparative genomic hybridization and single nucleotide polymorphism (CGH + SNP) array designed using Agilent technologies. This high-density array is designed to detect exonic and intronic copy number changes as small as 400 bp and 1.5kb, respectively, in the targeted gene(s). The analysis of the array hybridization data for targeted gene(s) is performed using Cytogenomics software (Agilent Technologies). These results may be confirmed by qPCR.

Utility: Affected individuals can benefit from screening and treatment regimens aimed at preventing the most serious complications of this condition. Asymptomatic relatives can have DNA screening to determine whether they will need extensive and expensive diagnostic evaluations.

Sensitivity: Approximately 96% of individuals who meet the Curaçao diagnostic criteria for HHT carry a detectable mutation in the coding sequence of either the ENG gene [HHT type 1] or the ACVRL1 gene [HHT type 2] (McDonald et al 2015). About 2-3% of individuals have a pathogenic variant in the SMAD4 gene, even without clinical features of juvenile polyposis. Sensitivity decreases when the number of clinical symptoms decreases or if there is no family history of HHT. Deep intronic mutations (in non-coding sequences) might not be detected by sequencing.

References:
McDonald et al. Front Genet. 2015 Jan 26;6:1.
Richards-Yutz et al. Hum Genet. 2010 Jul; 128(1):61-77

Name of Test	Turnaround Time	Cost	CPT codes
HHT: ENG/ACRVL1 Sequencing with reflex to Deletion/Duplication Analysis	6-8 weeks	$2,050*	81406, 81479x2, 81405
HHT: *ENG/ACRVL1* Sequencing with deletion/duplication analysis; if negative automatic reflex to *SMAD4* Sequencing and deletion/duplication	8-10 weeks	$2,650*	81406, 81479x2, 81405, 81406
HHT: ENG/ACRVL1 Deletion/Duplication Analysis	3-4 weeks	$750	81479, 81405
HHT: SMAD4 Deletion/Duplication Analysis	3-4 weeks	$750	81405
HHT: ENG/ACRVL1/SMAD4 Site Specific Analysis (familial)	2-3 weeks	$360	81403
HHT: ENG/ACRVL1/SMAD4 Site Specific Analysis (familial) (Prenatal)	7-10 days	$460	81403, 81265
HHT: SMAD4 Full Sequencing	8-10 weeks	$600	81406

***Reflex testing options**: Maximum cost is listed, although our lab only bills for the services performed. Final charge may be less than listed price, but cannot be determined until the testing has been completed.