Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hemorrhagic telangiectasia (HHT) or a related disorder

Second-tier testing for patients in whom previous targeted gene variant analyses for specific HHT genes were negative

Establishing a diagnosis of HHT and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved

Identifying variants within genes known to be associated with HHT and allowing for predictive testing of at-risk family members

Genetics Test Information

This test includes next-generation sequencing as well as supplemental Sanger sequencing to evaluate the genes listed on this panel.

Additionally, NGS is used to test for the presence of large deletions and duplications in a subset of genes.

Highlights

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate for variants in the *ACVRL1, ENG, GDF2, RASA1,* and *SMAD4* genes.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

Special Instructions

- Informed Consent for Genetic Testing
- Hereditary Hemorrhagic Telangiectasia (HHT) Gene Testing Patient Information
- Informed Consent for Genetic Testing (Spanish)

Method Name

Custom Sequence Capture and Targeted Next Generation Sequencing followed by qPCR or Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Advisory Information

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

1. Hereditary Hemorrhagic Telangiectasia (HHT) Gene Testing Patient Information **is required,** see Special Instructions. Testing may proceed without the patient information however it aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to complete the form and send it with the specimen.

2. Include physician name and phone number with specimen.

Specimen Required

Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimenin original tube.

Specimen Stability Information: Ambient (Preferred)/Refrigerated

Specimen Type: DNA

Container/Tube: 2 mL screw top tube

Specimen Volume: 100mcL (microliters)

Collection Instructions:

1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL.

2. Include concentration and volume on tube.

Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. If not ordering electronically, complete, print, and send a Cardiovascular Test Request Form (T724) with the

specimen.

Specimen Minimum Volume

Whole blood: 1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical and Interpretive

Clinical Information

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia characterized by the presence of arteriovenous malformations (AVM) of the skin, mucosa, and viscera. Small AVM, or telangiectasias, develop predominantly on the face, oral cavity, and hands, and spontaneous, recurrent epistaxis (nose bleeding) is a common presenting sign.

Symptomatic telangiectasias occur in the gastrointestinal tract of about 30% of HHT patients. Additional serious complications associated with HHT include transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage. These complications are a result of larger AVM, which are most commonly pulmonary, hepatic, or cerebral in origin, and occur in approximately 30%, 40%, and 10% of individuals with HHT, respectively.

HHT is inherited in an autosomal dominant manner and occurs with wide ethnic and geographic distribution. The overall incidence of HHT in North America is estimated to be between 1 in 5,000 and 1 in 10,000. Penetrance seems to be age related, with increased manifestations occurring over one's lifetime. For example, approximately 50% of diagnosed individuals report having nosebleeds by age 10 years, increasing to 80% to 90% by age 21 years, and as many as 90% to 95% of affected individuals eventually developing recurrent epistaxis.

HHT is phenotypically heterogeneous both between families and amongst affected members of the same family. Furthermore, complications associated with HHT have variable ranges of age of onset. Thus, HHT can be diagnostically challenging. Genetic testing allows for the confirmation of a suspected genetic disease. Confirmation of a diagnosis allows for proper treatment and management of the disease, preconception or prenatal counseling, and family counseling. In addition, it has been estimated that genetic screening of suspected HHT individuals and their families is more economically effective than conventional clinical screening.

Two genes are most commonly associated with HHT: the endoglin gene (*ENG*), and the activin A receptor, type II-like 1 gene (*ACVRL1* or *ALK1*). *ENG* and *ACVRL1* encode membrane glycoproteins involved in transforming growth factor-beta signaling related to vascular integrity. Variants in *ENG* are associated with HHT type 1 (HHT1), which has been reported to have a higher incidence of pulmonary AVM, whereas *ACVRL1* variants occur in HHT type 2 (HHT2), which has been reported to have a higher incidence of hepatic AVM.

The majority of variants in *ENG* and *ACVRL1* are missense, nonsense, splice site, or small intragenic deletions and insertions. Approximately 10% of *ENG* and *ACVRL1* variants are large genomic deletions and duplications (also known as dosage alterations). Approximately 60% to 80% of patients with HHT will have a variant detected in *ENG* or *ACVRL1*.

Pathogenic variants in the *SMAD4* gene are the third most common identifiable cause of HHT, accounting for approximately 10% of HHT patients who test negative for *ENG* and *ACVRL1*, and approximately 1% to 2% of total HHT cases. Pathogenic *SMAD4* variants cause autosomal dominant juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT), which includes features of juvenile polyposis syndrome (JPS) and HHT. JPS is characterized by hamartomatous polyps of the gastrointestinal tract and increased risk of gastrointestinal cancer. *SMAD4* variants have also been detected in families presenting with JPS or HHT only.

Pathogenic variants in the *GDF2* gene (also known as *BMP9*) are a rare cause of HHT. In a study of 191 individuals with clinically suspected HHT and no variants in *ENG*, *ACVRL1,* or *SMAD4*, 3 unrelated individuals were found to carry a rare missense variant in *GDF2*.Â

Pathogenic variants in the *RASA1* gene cause capillary malformation-arteriovenous malformation syndrome (CMAVM). CMAVM is characterized by the presence of multiple small (1-2 cm in diameter) capillary malformations mostly localized to the face and limbs. Patients may also have arteriovenous malformations (AVM) and arteriovenous fistulas (AVF). In some cases, pathogenic *RASA1* variants may be found in individuals clinically suspected to have HHT. Individuals with apathogenic *RASA1* variantmay have a clinical diagnosis of Parkes Weber syndrome (PWS), with multiple micro-AVF associated with a cutaneous capillary stain and excessive soft tissue and skeletal growth of an affected limb.

Table1.Â Genes included in the HHT Gene Panel

Gene Symbol (alias)	Protein	OMIM	Inheritance	Phenotype/Disorder
ACVRL1	Activin A receptor like type 1	601284	AD	Telangiectasia, hereditary hemorrhagic, type 2
ENG	Endoglin	131195	AD	Telangiectasia, hereditary hemorrhagic, type 1
GDF2	Growth differentiation factor 2	605120	AD	Telangiectasia, hereditary hemorrhagic, type 5
RASA1	RAS p21 protein activator 1	139150	AD	Capillary malformation-arteriovenous malformation, Parkes Weber syndrome
SMAD4	SMAD family member 4	600993	AD	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, Myhre syndrome

AD: autosomal dominant

AR: autosomal recessive

Reference Values

An interpretive report will be provided.

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variation that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of hereditary hemorrhagic telangiectasia (HHT) or a related disorder.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data.

Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a family history of HHT or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual would allow for more informative testing of at risk individuals.

Technical Limitations:

Next-generation sequencing may not detect all types of genetic variants. Additionally, rare polymorphisms may be present that could lead to false-negative or false-positive results. If the patient has had an allogeneic blood or marrow transplant or a recent (ie, less than 6 weeks from time of sample collection) heterologous blood transfusion, these results may be inaccurate due to the presence of donor DNA.

Reclassification of Variants Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of this patient's results.

Clinical Reference

1. McDonald J, Pyeritz RE: Hereditary Hemorrhagic Telangiectasia. In GeneReviews. Edited by Edited by RA Pagon, MP Adam, HH Ardinger, et al. University of Washington, Seattle. Accessed 2/16/18. Available at

www.ncbi.nlm.nih.gov/books/NBK1351/

2. Larsen Haidle J, Howe JR: Juvenile Polyposis Syndrome. In GeneReviews. Edited by Edited by RA Pagon, MP Adam, HH Ardinger, et al. University of Washington, Seattle. Accessed 2/16/18. Available at www.ncbi.nlm.nih.gov/books/NBK1469/

3. Bayrak-Toydemir P, Stevenson D: RASA1-Related Disorders. In GeneReviews. Edited by Edited by RA Pagon, MP Adam, HH Ardinger, et al. University of Washington, Seattle. Accessed 2/16/18. Available from: www.ncbi.nlm.nih.gov/books/NBK52764/

4. Cohen JH, Faughnan ME, Letarte M, et al: Cost comparison of genetic and clinical screening in families with hereditary hemorrhagic telangiectasia. Am J Med Genet A 2005 Aug 30;137(2):153-160

5. Sabba C, Pasculli G, Lenato GM, at al: Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 2007 Jun;5(6):1149-1157Â

6. Abdalla SA, Letarte M: Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. J Med Genet 2006 Feb;43(2):97-110

7. Guttmacher AE, Marchuk DA, White RI Jr: Hereditary hemorrhagic telangiectasia. N Engl J Med 1995 Oct 5;333(14):918-924

8. Bayrak-Toydemir P, Mao R, Lewin S, et al: Hereditary hemorrhagic telangiectasia: an overview of diagnosis and management in the molecular era for clinicians. Genet Med 2004;6:175-191

Performance

Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline for sequence variants and the presence of large intragenic deletions and duplications. Supplemental Sanger sequencing or qPCR may be performed occasionally in regions where NGS is insufficient for data capture or not specific enough to correctly identify a variant. Sanger sequencing or qPCR may also be used for confirmatory testing.(Unpublished Mayo method)

The following genes are evaluated in this multi-gene panel, *ACVRL1, ENG, GDF2, RASA1,* and *SMAD4.*

PDF Report

No

Day(s) and Time(s) Test Performed

Monday; Varies

Analytic Time

2 weeks

Maximum Laboratory Time

4 weeks

Specimen Retention Time

2 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81479

81406 x 2

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
HHTGP	Hereditary Hemorrhagic Telan Panel	35474-6

Result ID	Test Result Name	Result LOINC Value
601723	Gene(s) Evaluated	48018-6
601724	Result Summary	50397-9
601725	Result Details	82939-0
601726	Interpretation	69047-9
601727	Additional Information	48767-8
601728	Method	49549-9
601729	Disclaimer	62364-5
601730	Reviewed By	18771-6