

## Overview

### Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of hereditary hemorrhagic telangiectasia (HHT), cerebral cavernous malformation (CCM), capillary malformation-arteriovenous malformation syndrome (CV-AVM), or other hereditary vascular malformation syndromes of germline origin

Establishing a diagnosis of HHT, CCM, [CM-AVM](#), or other hereditary vascular malformation syndromes of germline origin

### Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 12 genes associated with hereditary hemorrhagic telangiectasia (HHT), cerebral cavernous malformation (CCM), capillary malformation-arteriovenous malformation syndrome (CM-AVM), and other hereditary vascular malformation syndromes of germline origin: *ACVRL1*, *BMPR2*, *CCM2*, *ENG*, *EPHB4*, *GDF2*, *GLMN*, *KRIT1*, *PDCD10*, *RASA1*, *SMAD4*, and *TEK*. See [Targeted Genes and Methodology Details for Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel](#) and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for HHT, CCM, CM-AVM, and other hereditary vascular malformation syndromes of germline origin.

[Prior Authorization](#) is available for this assay.

### Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)
- [Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel Patient Information](#)
- [Targeted Genes and Methodology Details for Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel](#)
- [HHT and Vascular Gene Panel \(HHTGG\) Prior Authorization Ordering Instructions](#)

### Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

### NY State Available

Yes

## Specimen

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**Specimen Type**

Varies

**Ordering Guidance**

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

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. To obtain more information about this testing option, call 800-533-1710.

**Shipping Instructions**

Specimen preferred to arrive within 96 hours of collection.

**Necessary Information**

[Prior Authorization](#) is available for this test. **Submit the required form with the specimen.**

**Specimen Required**

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**Specimen Type:** Whole blood

**Container/Tube:**

**Preferred:** Lavender top (EDTA) or yellow top (ACD)

**Acceptable:** Any anticoagulant

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**

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

**Forms**

1. **New York Clients-Informed consent is required.** Please document on the request form or electronic order that a copy is on file.

The following documents are available:

-[Informed Consent for Genetic Testing](#) (T576)

-[Informed Consent for Genetic Testing \(Spanish\)](#) (T826)

2. [Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel Patient Information](#)

3. [HHT and Vascular Gene Panel \(HHTGG\) Prior Authorization Ordering Instructions](#)

4. [If not ordering electronically, complete, print, and send a Cardiovascular Test Request Form](#) (T724) with the specimen.

**Specimen Minimum Volume**

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 & Interpretive****Clinical Information**

[Hereditary vascular malformation syndromes include a group of genetic conditions characterized by abnormal blood vessel development. These syndromes can be of germline or somatic origin. This gene panel is restricted to analysis of genes associated with vascular malformation syndromes of germline origin.](#)

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.(1) HHT has an estimated prevalence of 1:5000 and is primarily caused by heterozygous, disease-causing variants in the *ACVRL1* and *ENG* genes. Rarely, HHT can be caused by disease-causing variants in the *GDF2* gene (also known as *BMP9*). Additionally, *SMAD4* disease-causing variants cause autosomal dominant juvenile polyposis/HHT syndrome, which includes features of juvenile polyposis syndrome and HHT.(2) An overlapping pulmonary arterial hypertension and HHT phenotype have also been reported in association with the *BMPR2* gene.(3,4)

Familial cerebral cavernous malformation (CCM) is an autosomal dominant condition characterized by structurally abnormal capillaries in the central nervous system leading to an increased risk of cerebral hemorrhage.(5) The estimated prevalence of familial CCM ranges from 1:3300 to 1:10,000,(5) and the condition displays age-related penetrance with up to 50% of individuals remaining symptom free throughout their life.(5,6) Disease-causing variants in three genes have been associated with familial CCM: *KRIT1*, *CCM2*, and *PDCD10*.

Capillary malformation-arteriovenous malformation syndrome (CM-AVM) is an autosomal dominant condition primarily characterized by capillary malformations localized to the dermis of the face and limbs, AVM or arteriovenous fistulas of the skin, muscle, bone, spine, and brain, and Parkes Weber syndrome.(6) The prevalence of CM-AVM has been estimated in Northern European cohorts at approximately 1:100,000, with penetrance estimated at 90% to 99%.(6) Approximately 60% of cases of CM-AVM can be attributed to disease-causing variants in the *EPHB4* and *RASA1* genes. The genetic etiology remains unknown in approximately 40% of cases.(6)

Hereditary glomuvenous malformation is a rare autosomal dominant condition characterized by multiple venous malformations within the glomerulus of the kidney. The condition is associated with germline disease-causing variants in the *GLMN* gene. However, it is thought that a second, somatic (acquired) variant on the second allele, or acquired uniparental disomy, is required for the development of venous malformations.(7,8)

Multiple cutaneous and mucosal venous malformations (also known as cutaneomucosal venous malformation: VMCM) is an autosomal dominant condition characterized by small multifocal cutaneous and mucosal vascular malformations

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that typically present at birth.(9) These lesions are usually asymptomatic but may become painful if they are large enough to impact the underlying muscle tissue. The prevalence of this condition is unknown but thought to be rare. VMCM is associated with disease-causing variants in the *TEK* gene, and penetrance is estimated at 90% in individuals with a known genetic etiology.(9)

**Reference Values**

An interpretive report will be provided.

**Interpretation**

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Cautions**

Clinical Correlations:

Test results should be interpreted in the 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 clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:

Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:

This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

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This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Refer to the [Targeted Genes and Methodology Details for Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel](#) for the most up to date list of genes included in this test. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

#### Reclassification of Variants:

At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

#### Variant Evaluation:

Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.<sup>(10)</sup> Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

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 periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

#### Clinical Reference

1. Faughnan ME, Mager JJ, Hetts SW, et al: Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *Ann Intern Med.* 2020;173(12):989-1001. doi: 10.7326/M20-1443
2. McDonald J, Stevenson DA: Hereditary hemorrhagic telangiectasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds: *GeneReviews* [Internet]. University of Washington, Seattle; 2000. Updated November 24, 2021. Accessed July 26, 2022. Available at [www.ncbi.nlm.nih.gov/books/NBK1351/](http://www.ncbi.nlm.nih.gov/books/NBK1351/)
3. Rigelsky CM, Jennings C, Lehtonen R, Minai OA, Eng C, Aldred MA: BMP2 mutation in a patient with pulmonary arterial hypertension and suspected hereditary hemorrhagic telangiectasia. *Am J Med Genet A.* 2008 Oct;146A(19):2551-2556. doi: 10.1002/ajmg.a.32468
4. Ye F, Jiang W, Lin W, et al: A novel BMP2 mutation in a patient with heritable pulmonary arterial hypertension and

suspected hereditary hemorrhagic telangiectasia: A case report. *Medicine (Baltimore)*. 2020 Jul;99(31):e21342. doi: 10.1097/MD.00000000000021342

5. Zafar A, Quadri SA, Farooqui M, et al: [Familial cerebral cavernous malformations. \*Stroke\*. 2019 May;50\(5\):1294-1301. doi: 10.1161/STROKEAHA.118.022314](#)

6. Bayrak-Toydemir P, Stevenson DA: Capillary malformation-arteriovenous malformation syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews* [Internet]. University of Washington, Seattle; 2011. Updated September 12, 2019. Accessed July 26, 2022. Available at [www.ncbi.nlm.nih.gov/books/NBK52764/](http://www.ncbi.nlm.nih.gov/books/NBK52764/)

7. Brouillard P, Boon LM, Mulliken JB, et al: Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations ("glomangiomas"). *Am J Hum Genet*. 2002 Apr;70(4):866-874. doi: 10.1086/339492

8. Amyere M, Aerts V, Brouillard P, et al: Somatic uniparental isodisomy explains multifocality of glomuvenous malformations. *Am J Hum Genet*. 2013 Feb;92(2):188-196. doi: 10.1016/j.ajhg.2012.12.017

9. Boon LM, Vikkula M. Multiple cutaneous and mucosal venous malformations. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews* [Internet]. University of Washington, Seattle; 2008. Updated May 17, 2018. Accessed July 26, 2022. Available at [www.ncbi.nlm.nih.gov/books/NBK1967/](http://www.ncbi.nlm.nih.gov/books/NBK1967/)

10. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015 May;17(5):405-424. doi: 10.1038/gim.2015.30

## Performance

### Method Description

Next-generation sequencing (NGS) and Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See [Targeted Genes and Methodology Details for Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel](#) for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered. (Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *ACVRL1*, *BMPR2*, *CCM2*, *ENG*, *EPHB4*, *GDF2*, *GLMN*, *KRIT1*, *PDCD10*, *RASA1*, *SMAD4*, and *TEK*

### PDF Report

Supplemental

**Day(s) Performed**

Varies

**Report Available**

28 to 42 days

**Specimen Retention Time**

Whole blood: 2 weeks (if available); Extracted DNA: 3 months

**Performing Laboratory Location**

Rochester

**Fees & 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 account representative. 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 US Food and Drug Administration.

**CPT Code Information**

81406 x3

81479

**Prior Authorization**

Insurance preauthorization is available for this testing; forms are available.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.

**LOINC® Information**

Test ID	Test Order Name	Order LOINC® Value
HHTGG	HHT and Vascular Gene Panel	51966-0

Result ID	Test Result Name	Result LOINC® Value
617296	Test Description	62364-5
617297	Specimen	31208-2
617298	Source	31208-2

## Test Definition: HHTGG

Hereditary Hemorrhagic Telangiectasia and  
Vascular Malformations Gene Panel, Varies

617299	Result Summary	50397-9
617300	Result	82939-0
617301	Interpretation	69047-9
617302	Additional Results	In Process
617303	Resources	99622-3
617304	Additional Information	48767-8
617305	Method	85069-3
617306	Genes Analyzed	48018-6
617307	Disclaimer	62364-5
617308	Released By	18771-6