Test Definition: VHLZZ

Von Hippel Lindau Syndrome, VHL, Full Gene Analysis, Varies

Overview

Useful For

Evaluating patients with a personal or family history suggestive of Von Hippel-Lindau (VHL) syndrome

Establishing a diagnosis of a VHL allowing for targeted cancer surveillance based on associated risks

Identifying genetic variants associated with increased risk for VHL syndrome allowing for predictive testing of at-risk family members

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in the *VHL* gene associated with Von Hippel-Lindau (VHL) syndrome. See Method Description and Gene Selection Table for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for VHL syndrome.

Special Instructions

- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

For patients suspected of having hereditary erythrocytosis, order NHEP / Hereditary Erythrocytosis Gene Panel, Next-Generation Sequencing, Varies.

For a comprehensive hereditary cancer panel that includes the *VHL* gene, consider one of the following tests:

-ENDCP / Hereditary Endocrine Cancer Panel, Varies
-HPGLP / Hereditary Paraganglioma/Pheochromocytoma Panel, Varies
-RENCP / Hereditary Renal Cancer Panel, Varies

Testing for *VHL* gene as part of a customized panel is 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 this gene. For more information see FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

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: Green top (Sodium heparin)
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 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for samples received after 4 days and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies:
DNA Saliva Kit High Yield (T1007)
Saliva Swab Collection Kit (T786)
Container/Tube:
Preferred: High-yield DNA saliva kit
Acceptable: Saliva swab
Specimen Volume: 1 Tube if using T1007 or 2 swabs if using T786
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

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:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Molecular Genetics: Inherited Cancer Syndromes Patient Information Sheet (T519)
3. If not ordering electronically, complete, print, and send a Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume

Whole blood: 1 mL; Saliva: See Specimen Required

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

Germline variants in the *VHL* gene are associated with Von Hippel-Lindau (VHL) syndrome, a rare autosomal dominant hereditary cancer syndrome.(1,2) VHL syndrome is characterized by an increased risk of developing a variety of cancerous and non-cancerous tumors and lesions, including hemangioblastomas of the brain or spinal cord, retinal angiomas, renal, pancreatic and epididymal cysts, pheochromocytomas, pancreatic neuroendocrine tumors, endolymphatic cell tumors, and clear cell renal cell carcinoma.(3) While considered a highly penetrant condition, approximately 20% of VHL syndrome cases are due to new (*de novo*) disease-causing variants, which, in some cases, result in disease mosaicism.(4)

Research has suggested certain combinations of VHL tumors cluster in VHL families, and this may be driven by the type of VHL gene variant present in the family.(4) This observation has led to a phenotype-based classification of VHL syndrome. However, these patterns are not entirely specific and should not necessarily be used for diagnostic or therapeutic purposes.

The National Comprehensive Cancer Network provides recommendations regarding the medical management of individuals with VHL syndrome.

Of note, germline variants in the *VHL* gene are also associated with autosomal recessive hereditary erythrocytosis or polycythemia. Cases of VHL cancer syndrome and erythrocytosis are largely mutually exclusive, although there is some overlap. For information regarding genetic testing for patients suspected to have hereditary erythrocytosis or polycythemia, see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) 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.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR /

Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

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.

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 heterologous 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:
Currently, 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. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

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.(5) 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. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. OMIM: 193300. Von Hippel-Lindau Syndrome; VHLS. Johns Hopkins University; 1986. Updated June 4, 2020. Accessed September 9, 2024. Available at https://omim.org/entry/193300
2. Beroud C, Collod-Beroud G, Boileau C, Soussi T, Junien C. UMD-VHL mutations database. The Universal Mutation Database (UMD); Accessed July 7, 2021. Available at www.umd.be
3. van Leeuwaarde RS, Ahmad S, Links TP, Giles RH. Von Hippel-Lindau syndrome. In: Adam MP, Everman DB, Mirzaa GM et al, eds. GeneReviews. [Internet]. University of Washington, Seattle; 2000. Updated February 29, 2024. Accessed

September 9, 2024. Available at: www.ncbi.nlm.nih.gov/books/NBK1463/
4. Lonser RR, Glenn GM, McClellan W, et al. von Hippel-Lindau disease. Lancet. 2003;361(9374):2059-2067
5. 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;17(5):405-424

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the *VHL* gene, 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 deletion-insertions (delins) less than 40 base pairs (bp), and above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the *VHL* gene.

There may be regions of the *VHL* gene 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 content, and repetitive sequences. For more information, see the Gene Selection Table. The reference transcript for *VHL* gene is NM_000551.3. Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing.(Unpublished Mayo method)

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

PDF Report

No

Day(s) Performed

Varies

Report Available

21 to 28 days

Specimen Retention Time

Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Saliva: 1 month

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Test Definition: VHLZZ

Von Hippel Lindau Syndrome, VHL, Full Gene Analysis, Varies

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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81404

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
VHLZZ	VHL Full Gene Analysis	82533-1

Result ID	Test Result Name	Result LOINC® Value
614875	Test Description	62364-5
614876	Specimen	31208-2
614877	Source	31208-2
614878	Result Summary	50397-9
614879	Result	82939-0
614880	Interpretation	69047-9
614881	Resources	99622-3
614882	Additional Information	48767-8
614883	Method	85069-3
614884	Genes Analyzed	48018-6
614885	Disclaimer	62364-5
614886	Released By	18771-6