Von Hippel-Lindau Disease Genetic Testing

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Introduction

Von Hippel-Lindau (VHL) disease genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
VHL deletion/duplication analysis	81403
VHL known familial mutation analysis	81403
VHL sequencing	S3842
	81404

Criteria

Introduction

Requests for genetic testing for Von Hippel-Lindau disease (VHL) are reviewed using the following criteria.

VHL Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous VHL gene testing that would detect the familial mutation, AND
- Diagnostic and Predisposition Testing:

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  - Known family mutation in VHL identified in 1st degree relative(s). (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

VHL Sequencing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous VHL gene sequencing, and
  - No known familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - A positive family history of VHL and a personal history of one or more of the following:
    - Spinal or cerebellar hemangioblastoma, or
    - Retinal hemangioblastoma, or
    - Renal cell carcinoma, or
    - Pheochromocytoma, or
    - Paraganglioma, or
    - Multiple renal and/or pancreatic cysts, or
    - Endolymphatic sac tumor (ELST), or
    - Pancreatic neuroendocrine tumor (PNET), OR
  - No known family history of VHL-related findings and meets one of the following:
    - Two or more hemangioblastomas involving the retina, spine, and/or brain, or
    - A single hemangioblastoma and a characteristic visceral mass (such as renal cell carcinoma, pheochromocytoma, paraganglioma, endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumors of the pancreas), OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - A first-degree relative of someone with a clinical diagnosis of VHL who has had no previous genetic testing (Note that testing in the setting of a more distant affected relative will only be considered if the first-degree relative is unavailable or unwilling to be tested); AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

VHL Deletion/Duplication Analysis

- Genetic Counseling:

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  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - There is no known familial mutation, and
  - No previous deletion/duplication analysis of the VHL gene has been performed, and
  - Above criteria for VHL full gene sequence analysis are met, and
  - VHL sequencing was previously performed and no mutations were found, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

VHL testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

What is Von Hippel-Lindau Disease?

Von Hippel-Lindau disease (VHL) is a hereditary cancer syndrome. The main clinical features include hemangioblastomas of the central nervous system (CNS) and retina, renal cysts and renal cell carcinoma, pancreatic cysts and neuroendocrine tumors, pheochromocytomas and paragangliomas, endolymphatic sac tumors, and epididymal and broad ligament cysts.[1]

Incidence

The incidence of VHL is 1 in 36,000 people.[1]

Symptoms

Various cancers and tumors may be seen with VHL.

- The cardinal feature of VHL is hemangioblastoma. CNS hemangioblastomas present in 60%-80% of individuals, and retinal hemangioblastomas present in about 70% of individuals.[1,2] CNS hemangioblastomas are the main cause of death for individuals with VHL.[3]
- The risk to develop clear cell renal carcinoma by age 60 is as high as 70%, and this is the leading cause of mortality for individuals with VHL.[1-3]
- Pheochromocytomas may cause sustained or episodic hypertension or may not cause signs/symptoms; they are usually benign. Pheochromocytomas have been reported in up to 35% of individuals with VHL. [3] Additionally, the presence or absence of pheochromocytomas can be correlated with certain genotypes.[1,3]

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Paragangliomas can develop along the sympathetic axis in the abdomen or thorax and are often nonfunctional (i.e., do not secrete catecholamines or other hormones).[1] Paragangliomas have been described in up to 12% of individuals with VHL.[3]

- Endolymphatic sac tumors are seen in approximately 10-16% of individuals with VHL, and in some instances unilateral or bilateral hearing loss is the initial clinical manifestation of VHL.[1]
- Epididymal tumors have also been reported in VHL. Males with bilateral epididymal tumors may have infertility.[1]
- Clinical findings of VHL may include vision loss, hearing loss, gait disturbance, pain and sensory motor loss depending on the location of the tumor.[1]
- Almost all individuals with a VHL gene mutation show symptoms of the disease by age 65.[1] Age of onset, disease severity, and tumor types vary between and within affected families.

Cause

VHL is caused by mutations in the VHL gene. More than 1500 germline and sporadic VHL gene mutations have been identified. The VHL gene is a tumor suppressor whose normal role is to control cell growth and proliferation.[1,4] VHL mutations lead to a loss of function of the gene and an increased risk for uncontrolled growth of tumors and cysts.[1]

Inheritance

VHL is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Most (80%) of VHL mutations are inherited (germline), and about 20% are new (de novo) mutations.[1]

VHL mutations inherited in an autosomal recessive manner cause familial erythrocytosis type 2.[1] Testing for familial erythrocytosis type 2 is not addressed in this guideline.

Diagnosis

"The diagnosis of von Hippel-Lindau (VHL) syndrome is established in a proband who fulfills existing diagnostic clinical criteria. Identification of a heterozygous germline VHL pathogenic variant on molecular genetic testing establishes the diagnosis if clinical features are inconclusive."[1]

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Full sequence analysis assesses all three exons of the VHL gene and will detect about 85% of mutations.[1]

VHL deletion/duplication analysis detects partial or complete gene deletions which account for about 10% of VHL mutations.[1]

Approximately 5% of individuals with a clinical diagnosis of VHL do not have a mutation identified.[1]

Management

Surveillance recommendations for individuals diagnosed with or at-risk for inheriting VHL include ophthalmologic exams, CNS and inner ear MRI, abdominal imaging, blood pressure monitoring, blood or urinary fractionated metanephrines, and audiologic evaluation.[1,3] "The surveillance recommendations are age-dependent, as the frequency of new tumour development as well as growth of exiting tumours vary significantly with age."[3] Some of the screenings should begin at one year of age in at-risk/affected individuals.[4,5] Early detection of VHL tumors may lead to improved outcome.[1] However, at-risk individuals can forego screening if genetic testing for a known familial mutation is performed and they have a normal (negative) result.[1,2]

Belzutifan is an oral medication approved by the FDA for treatment in individuals with VHL who have renal cell carcinoma, central nervous system hemangioblastoma or a pancreatic neuroendocrine tumor, not requiring immediate surgery.[6] This medication targets hypoxia-inducible factor-2 alpha (HIF2a) which contributes to tumor growth. "After 18 months, nearly half of the participants had kidney tumor shrinkage of at least 30% (a partial response), and a majority of those people's tumors were still responding after 1 year. Belzutifan also shrank VHL-associated brain, pancreatic, and eye tumors."[6]

Survival

In a retrospective cohort study, "the estimated mean life expectancies for male and female patients born in 2000 were 67 and 60 years, respectively. Overall, 79% (53 of 67) of the deaths were vHL-related, but the risk of vHL-related death has decreased over time, as has the frequency of renal cell carcinoma (RCC)-related death."[7]

Test information

Introduction

Testing for VHL may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Laboratories may perform only next generation sequencing, sequencing with reflex to deletion/duplication analysis or sequencing and deletion/duplication analysis concurrently.

Guidelines and evidence

American Society of Clinical Oncology

A position statement by the American Society of Clinical Oncology (ASCO, 1996) considered VHL a Group 1 disorder: "Tests for families with well-defined hereditary syndromes for either a positive or negative result will change medical or prenatal management, and for whom genetic testing may be utilized as part of the routine medical care."[8]

The American Society of Clinical Oncology (ASCO, 2003) stated the following regarding genetic testing in affected and at-risk children:[9]

- “ASCO recommends that the decision to offer testing to potentially affected children should take into account the availability of evidence-based risk-reduction strategies

and the probability of developing a malignancy during childhood. Where risk-reduction strategies are available or cancer predominantly develops in childhood, ASCO believes that the scope of parental authority encompasses the right to decide for or against testing."

The American Society of Clinical Oncology (ASCO, 2010 and 2015) published policy statements regarding genetic and genomic testing for cancer susceptibility.[10,11] Although each addressed certain recommendations, VHL is not specifically mentioned in these statements.

The American Society of Clinical Oncology (ASCO, 2024) published a guideline regarding selection of germline genetic testing panels in individuals with cancer. This provided guidance on VHL germline testing.[12]

- The guidance regarding genes recommended for testing and inclusion in multigene panels stated that VHL germline testing was "more strongly recommended (higher relative risk of cancer or highly actionable)" for pheochromocytomas, paragangliomas and renal cell carcinomas.[12]
- The guidance regarding germline testing after a mutation was identified on tumor testing stated that VHL germline testing was in the category of genes that would prompt germline testing if a mutation is identified on tumor testing. However, an exclusion is if a mutation in the VHL gene was identified in a renal cell carcinoma.[12] This alone would not prompt germline testing due to the high prevalence of acquired somatic mutations in renal cell carcinomas.[13]

Selected Relevant Publications

A 2024 expert-authored review stated the following with regard to diagnosing VHL:[1]

- "The clinical sensitivity of molecular genetic testing of VHL makes it possible to effectively rule out von Hippel-Lindau (VHL) syndrome with a high degree of certainty in individuals with (1) isolated hemangioblastoma, retinal angioma, or clear cell renal cell carcinoma and (2) no detectable germline VHL pathogenic variant. Somatic mosaicism for a VHL pathogenic variant could still be considered in such individuals (an estimated 5% of individuals with VHL have somatic mosaicism)."
- Diagnostic testing can be accomplished through single gene testing when the phenotype, laboratory analysis and imaging suggest the diagnosis of VHL.
- At-Risk Relatives: "If the VHL pathogenic variant in the family is known, molecular genetic testing can be used for early identification of at-risk family members to improve diagnostic certainty and reduce the need for screening procedures in those at-risk family members who have not inherited the pathogenic variant."

Clinical diagnostic criteria can guide germline testing of VHL. A clinical diagnosis of VHL is supported in the literature when an individual with a family history of VHL has at least one VHL manifestation. In an individual without a family history of VHL, a diagnosis is supported when an individual has at least two VHL manifestations of which at least one is a hemangioblastoma.[3,14-18] Typical VHL tumors are retinal and cerebellar

hemangioblastomas, renal cell carcinomas, pheochromocytomas, paragangliomas, endolymphatic sac tumors, and pancreatic neuroendocrine tumors.[3,15-18] The presence of a single or multiple pancreatic or renal cyst(s) or papillary cystadenoma in the epididymis/ papillary cystadenoma of the broad uterine ligament may heighten the suspicion for VHL but are not included in the current diagnostic criteria.[3,14,17]

A peer reviewed 2016 article recommended: "Although the average age of onset of VHL tumors is in the third decade of life, some patients develop tumors at age younger than 10 years and as early as infancy; therefore, presymptomatic genetic testing for VHL is justified, and also may identify those children who did not inherit the familial VHL mutation, thus sparing them from a lifetime of clinical screening...[it] is strongly recommended that genetic counseling for presymptomatic genetic testing be conducted by a genetics professional in a comfortable environment and with the option of having multiple genetic counseling sessions as necessary."[15]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Von Hippel-Lindau disease testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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