Von Hippel-Lindau Disease Testing

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.

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What is Von Hippel-Lindau (VHL) syndrome

Definition

Von Hippel-Lindau (VHL) syndrome is a hereditary cancer syndrome.

- Von Hippel-Lindau (VHL) syndrome is a hereditary cancer syndrome whose main clinical features include hemangioblastomas of the central nervous system (CNS) and retina, renal cysts and renal cell carcinoma, pheochromocytoma, and endolymphatic sac tumors.\(^1\)
  - The cardinal feature of VHL syndrome is hemangioblastoma. CNS hemangioblastomas present in 60%-80% of individuals, and retinal hemangioblastomas present in about 70-80% of individuals.\(^1,2\)
  - The risk to develop clear cell renal carcinoma by age 60 is as high as 70%, and is the leading cause of death for individuals with VHL syndrome.\(^1,2\)
  - Pheochromocytomas and endolymphatic sac tumors are less commonly seen in VHL syndrome than other manifestations.
  - 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.\(^1\)
- The incidence of VHL is 1 in 36,000 people.\(^1\)
VHL syndrome 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.\(^1\) VHL mutations lead to a loss of function of the gene and an increased risk for uncontrolled growth of tumors and cysts.\(^1\)

Most (80%) of VHL mutations are inherited (germline), and about 20% are new (de novo) mutations.\(^1\) VHL syndrome is an autosomal dominant condition with children of affected individuals having a 50% chance of inheriting the disease-causing mutation.\(^1\)

Almost 100% of 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.

Surveillance recommendations for individuals diagnosed with or at-risk for inheriting VHL syndrome include annual ophthalmologic exams, MRI of the brain and total spine every two years starting at age 16 years, annual abdominal ultrasound, MRI of the abdomen every two years starting at 16 years, annual blood pressure monitoring, annual blood or urinary fractionated metanephrines starting at 5 years, and audiologic evaluation. Some of the screenings should begin at one year of age in at-risk/affected individuals.\(^3,4\) 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.\(^1,2\)

**Test information**

**VHL full gene sequence analysis** checks all three exons and will detect about 89% of mutations.\(^1\) Some laboratories perform only sequencing, while others do sequencing with reflex to deletion/duplication analysis or perform sequencing and deletion/duplication analysis concurrently.

**VHL deletion/duplication analysis** detects partial or complete gene deletions which account for about 11% of VHL mutations.\(^1\)

**VHL known familial mutation analysis:** Once a VHL mutation is identified in an affected person, predictive testing is available for at-risk family members, as is prenatal or preimplantation genetic diagnosis.\(^1\) Family members should be tested using the method that can accurately identify the familial mutation. This testing is typically less expensive than a full gene evaluation and provides clear results about whether the family member is predisposed to developing VHL syndrome.\(^1\)

**Guidelines and evidence**

A 2018 expert-authored review states the following with regard to diagnosing VHL: \(^1\)

- "The diagnosis of von Hippel-Lindau (VHL) syndrome is established in a proband with... clinical features... and/or by identification of a heterozygous
germline pathogenic variant in VHL on molecular genetic testing. Identification of a heterozygous germline pathogenic variant in VHL by molecular genetic testing establishes the diagnosis and supports periodic follow up even if clinical and radiographic features are nonconclusive."

- "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 or a VHL pathogenic variant could still be considered in such individuals."

- 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."

- Consensus-based clinical diagnostic guidelines state that the diagnosis of VHL can be made in the following circumstances:5

  - "Patients with a family history, and a CNS haemangioblastoma (including retinal haemangioblastomas), phaeochromocytoma, or clear cell renal carcinoma are diagnosed with the disease."

  - "Those with no relevant family history must have two or more CNS haemangioblastomas, or one CNS haemangioblastoma and a visceral tumour (with the exception of epididymal and renal cysts, which are frequent in the general population) to meet the diagnostic criteria."

- The American Society of Clinical Oncologists (ASCO) position statement on genetic testing (originally published 19966; revised/affirmed in 20037, 20108, and 20159) considers VHL syndrome 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.”

- The 2003 update specifically addresses issues around genetic testing in affected and at-risk children:
  - “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.”
A peer reviewed 2016 article recommends: “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.”

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 have detected the family mutation, AND

- Diagnostic and Predisposition Testing:**
  - 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

** Includes prenatal testing for at-risk pregnancies.

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
- Spinal or cerebellar hemangioblastoma, or
- Retinal hemangioblastoma, or
- Renal cell carcinoma, or
- Pheochromocytoma, or
- Multiple renal and/or pancreatic cysts, OR

  - No known family history of VHL-related findings, and
    - 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, 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:
  - 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.

References


