Test Specific Guidelines

Von Hippel-Lindau Disease Genetic Testing

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Introduction

Von Hippel-Lindau testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
VHL Deletion/Duplication Analysis	81403
VHL Known Familial Mutation Analysis	81403
VHL Sequencing	S3842
	81404

What Is Von Hippel-Lindau Syndrome?

Definition

Von Hippel-Lindau (VHL) syndrome 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, pheochromocytoma, and endolymphatic sac tumors.[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 syndrome is hemangioblastoma. CNS hemangioblastomas present in 60%-80% of individuals, and retinal hemangioblastomas present in about 70% 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.[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 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.

Cause

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.[1,3] 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 syndrome 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 identification of a pathogenic mutation in the VHL gene establishes the diagnosis.[1]

Full sequence analysis assesses all three exons of the VHL gene and will detect about 89% of mutations.[1]

VHL deletion/duplication analysis detects partial or complete gene deletions which account for about 11% of VHL mutations.[1]

Management

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 starting at age 8 years, 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.[1] 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]

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.[5] 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."[5]

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."[6]

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.

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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

Introduction

This section includes relevant guidelines are evidence pertaining to VHL testing.

American Society of Clinical Oncologists

A position statement by the American Society of Clinical Oncologists (ASCO, 1996) considered 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.” [7]

The American Society of Clinical Oncologist (ASCO, 2003) stated the following regarding genetic testing in affected and at-risk children:[8]

“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 Oncologist (ASCO, 2010 and 2015) published policy statements regarding genetic and genomic testing for cancer susceptibility.[9,10] Although each addressed certain recommendations, VHL is not specifically mentioned in these statements.

Selected Relevant Publications

A 2018 expert-authored review stated 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 stated that the diagnosis of VHL can be made in the following circumstances:[11]

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."

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."[12]

Criteria

Introduction

Requests for genetic testing for VHL are reviewed using these 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

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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.

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 address here.

References

Introduction

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