Coverage Policy

Please refer to the applicable benefit plan document to determine benefit availability and the terms, conditions and limitations of coverage. Under some benefit plans, coverage for genetic screening and/or testing may be excluded or restricted. If coverage for genetic testing is available, the following conditions of coverage apply.

Cigna covers genetic testing for von Hippel-Lindau (VHL) disease as medically necessary for ANY of the following indications:

- confirmatory (i.e., diagnostic) testing with full sequence analysis (gene VHL) in individuals with known or suspected VHL-associated tumor or VHL syndrome
- confirmatory (i.e., diagnostic) testing with deletion/duplication analysis (gene VHL) when full sequence analysis is negative and clinical suspicion of the condition remains high
- testing for known familial mutation (i.e., testing for the known familial variant) (gene VHL) for EITHER of the following:
  - predictive testing of at-risk family members once a disease-causing germline mutation has been identified in a blood relative
  - prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when the disease-causing mutation has been identified in a first- or second-degree relative*

* A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.
*A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

Cigna does not cover genetic testing for VHL disease in the general population because such screening is considered not medically necessary.

Any individual undergoing genetic testing for VHL disease should have both pre-and post-test genetic counseling completed by ONE of the following:

- an independent Board-Certified or Board-Eligible Medical Geneticist
- an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
- a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

General Background

Von Hippel-Lindau (VHL) disease or syndrome is an inherited multisystem disorder characterized by abnormal growth of blood vessels. VHL is characterized by hemangioblastomas of the brain, spinal cord and retinas; renal cysts and clear cell renal cell carcinomas; pheochromocytomas; and endolymphatic sac tumors. The gene for VHL is inherited in an autosomal dominant manner. It is estimated that 80% of individuals with VHL syndrome have an affected parent, and approximately 20% have VHL syndrome as the result of a de novo gene mutation. Mutations of the VHL gene have a high penetrance with almost all individuals with a mutation exhibiting disease-related symptoms by age 65 years (Frantzen, et al., 2012).

The VHL gene is a tumor suppressor that is the only gene known to be associated with the disease. When the gene is lost or mutated, its inhibitory effect on cell growth is lost or diminished and can lead to cancerous growth. Von Hippel-Lindau (VHL) disease is characterized by hemangioblastomas of the brain, spinal cord, and retina; renal cysts and clear cell renal cell carcinoma; pheochromocytoma, pancreatic cysts and neuroendocrine tumors; endolymphatic sac tumors; and epididymal and broad ligament cysts. Cerebellar hemangioblastomas may be associated with headache, vomiting and gait disturbances or ataxia. Retinal hemangioblastomas may be the initial manifestation of VHL syndrome and can cause vision loss. Renal cell carcinoma occurs in about 70% of affected individuals by age 60 years, and is a leading cause of mortality in VHL disease. Pheochromocytomas may be asymptomatic but can cause sustained or episodic hypertension. Endolymphatic sac tumors can cause hearing loss of varying severity, which can be a presenting symptom. Early recognition of VHL syndrome may allow for timely intervention and improved outcome (Frantzen, et al., 2012).

The clinical diagnosis of von Hippel-Lindau (VHL) disease is established in (Frantzen, et al., 2012):

- A simplex case (i.e., an individual with no known family history of VHL disease) presenting with two or more characteristic lesions:
  - Two or more hemangioblastomas of the retina, spine, or brain or a single hemangioblastoma in association with a visceral manifestation (e.g., multiple kidney or pancreatic cysts)
  - Renal cell carcinoma
  - Adrenal or extra-adrenal pheochromocytomas
  - Less commonly, endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumors of the pancreas
- An individual with a positive family history of VHL disease in whom one or more of the following disease manifestations is present:
- Retinal angioma
- Spinal or cerebellar hemangioblastoma
- Adrenal or extra-adrenal pheochromocytoma
- Renal cell carcinoma
- Multiple renal and pancreatic cysts

Note: Other lesions characteristic of VHL are endolymphatic sac tumors (ELST) and pancreatic neuroendocrine tumors; however these are not typically used to make a clinical diagnosis of VHL.

Regarding renal cell carcinoma, consideration should be given to the age of the patient. In general, VHL should be considered when renal cell carcinoma presents in younger patient (National Comprehensive Cancer Network® [NCCN]; National Cancer Institute [NCI], 2014). The NCCN guidelines for kidney cancer note, “[renal cell carcinoma] RCC in younger patients may indicate VHL disease, and these patients should be referred to a hereditary cancer clinic for further evaluation.” (NCCN, 2014)

Four general VHL disease phenotypes have been described, based on the likelihood of pheochromocytoma or renal cell carcinoma (Frantzen, et al., 2012). VHL type 1 is characterized by a low risk for pheochromocytoma. VHL type 2 is characterized by a high risk for pheochromocytoma and is further subdivided into:

- Type 2A: This type is characterized by a low risk of renal cell carcinoma.
- Type 2B: This type carries a high risk of renal carcinoma.
- Type 2C: This type carries a risk for pheochromocytoma only.

Individuals with known VHL syndrome, individuals without clinical manifestations but known to have a VHL disease-causing mutation, and at-risk relatives who have not undergone DNA testing need regular clinical monitoring by a physician or medical team familiar with the spectrum of VHL syndrome. Surveillance of these individuals includes the following (Frantzen, et al., 2012):

- Starting at age one year: annual evaluation for neurologic symptoms, vision problems, and hearing disturbance; annual blood pressure monitoring; annual ophthalmology evaluation.
- Starting at age five years: annual blood or urinary fractionated metanephrines; audiology assessment every two to three years; thin-slice MRI with contrast of the internal auditory canal in those with repeated ear infections.
- Starting at age 16 years: annual abdominal ultrasound and every other year MRI scan of the abdomen; MRI of the brain and total spine every two years.

Treatment of manifestations of conditions (i.e., such as hemangioblastomas of the nervous system and retina, renal cell carcinomas, pheochromocytomas, and endolymphatic sac tumors) usually include surgical removal. Epididymal or broad ligament papillary cyst adenomas generally do not require surgery. Early detection through surveillance and removal of tumors may prevent or minimize deficits such as hearing loss, vision loss and neurological symptoms.

Genetic Testing
Molecular genetic testing of the VHL gene detects mutations in nearly 100% of affected individuals with suspected or known VHL syndrome for confirmation of the diagnosis. Molecular genetic testing is indicated for all individuals known to have or suspected of having VHL syndrome. For individuals with manifestations of VHL syndrome who do not meet strict diagnostic criteria and who do not have a detectable VHL germline mutation, somatic mosaicism for a de novo VHL disease-causing mutation should be considered (Sgambati, et al., 2000).

Molecular genetic testing of at-risk family members is appropriate in order to determine the need for continued clinical surveillance when a disease-causing germline mutation has been identified in an affected family member. Those who have the disease-causing mutation would require regular surveillance, whereas family members who have not inherited the disease-causing mutation and their offspring would not.

Because early detection of at-risk individuals affects medical management, testing of individuals during childhood who have no symptoms is beneficial (American Society of Clinical Oncology [ASCO], 2003). Since
ophthalmological screening for those at risk for VHL begins before age five, molecular genetic testing may be considered in young children if the results would alter the medical management.

Full sequence analysis of the VHL gene can detect mutation by approximately 72%. When sequence analysis is negative, deletion/duplication analysis can be performed to detect partial or whole-gene deletion. Deletion/duplication analysis may use a variety of methods that includes: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment (Frantzen, et al., 2012).

Genetic testing should be undertaken only after independent genetic counseling has been provided to patients in order to assist in complex clinical decision-making. Post-genetic testing counseling should be planned.

Prenatal Testing and Preimplantation Genetic Diagnosis (PGD): Prenatal diagnosis for pregnancies at 50% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis, usually performed at about 15-18 weeks’ gestation, or chorionic villus sampling (CVS), at about 10-12 weeks’ gestation. The VHL disease-causing allele of an affected family member must be identified before prenatal testing or PGD can be performed.

Professional Societies/Organizations
American Society of Clinical Oncology (ASCO): ASCO policy on genetic testing for cancer susceptibility recommends that genetic testing be offered when:

- the individual has personal or family history features suggestive of a genetic cancer susceptibility condition
- the test can be adequately interpreted
- the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer

The policy recommends that genetic testing only be done in the setting of pre- and post-test counseling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities. (ASCO, 2003/ Robson, et al., 2010)

National Society of Genetic Counselors (NSGC): published recommendations for essential elements of genetic cancer risk assessment. Genetic testing should be offered when the following conditions apply (Riley, et al., 2012):

- An individual has a personal or family history suggestive of an inherited cancer syndrome.
- The genetic test can be adequately interpreted.
- Testing will influence medical management of the patient or other relatives.
- The potential benefits of testing outweigh the potential risks.
- Testing is voluntary.
- The individual seeking testing or their legal proxy can provide informed consent.

Use Outside of the US
No relevant information

Summary
Molecular genetic testing is indicated to confirm a diagnosis in individuals who are known to have or suspected of having von Hippel-Lindau (VHL) disease or syndrome and to evaluate individuals with a single VHL-associated tumor and a negative family history of the disease; for predictive testing of an at-risk family member in order to determine the need for continued clinical surveillance after the disease-causing germline mutations are identified in an affected family member; and for prenatal testing and preimplantation genetic diagnosis when the disease-causing germline mutations have been identified in a first- or second-degree relative.

Coding/Billing Information
Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary:

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<th>CPT® Codes</th>
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| 81403      | Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)  
  - VHL (von Hippel-Lindau tumor suppressor) (eg, von Hippel-Lindau familial cancer syndrome), deletionduplication analysis  
  - Known familial variant, not otherwise specified, for gene listed in Tier 1 or Tier 2, DNA sequence analysis, each variant exon |
| 81404      | Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)  
  - VHL (von Hippel-Lindau tumor suppressor) (eg, von Hippel-Lindau familial cancer syndrome), full gene sequence |

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<td>S3842</td>
<td>Genetic testing for von hippel-lindau disease</td>
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References


