



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Genetic Testing for von Hippel-Lindau Disease

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Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	3
References	4
Policy History	5

Hyperlink to Related Coverage Policies

- Genetic Counseling
- Genetic Disease Screening Panels
- Genetic Testing of Heritable Disorders
- Preimplantation Genetic Diagnosis

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

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

- confirmatory testing in individuals with known or suspected VHL-associated tumor or VHL syndrome
- predictive testing of at-risk family members once a disease-causing germline mutation has been identified in an affected first- or second-degree 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.

An individual undergoing genetic testing for any reason should have both pre- and post- test genetic counseling with a physician or a licensed or certified genetic counselor.

CIGNA does not cover genetic testing for VHL disease in the general population because such screening is considered not medically necessary or of unproven benefit.

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 (Schimke, et al., 2009).

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. VHL appears to act as a gatekeeper to a multistep process of tumor genesis. 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 40% of affected individuals with VHL and is the leading cause of mortality. 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 (Schimke, et al., 2009).

Four general VHL disease phenotypes have been described, based on the likelihood of pheochromocytoma or renal cell carcinoma (Schimke, et al., 2009). 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. Monitoring of these individuals includes the following (Schimke, et al., 2009):

- annual ophthalmological screening, preferably beginning before age five
- annual blood pressure monitoring, supplemented by measurement of urinary catecholamine metabolites beginning at age five in those families with a high incidence of pheochromocytoma
- annual abdominal ultrasound examination beginning at age 16
- suspicious lesions in the kidney, adrenal gland or pancreas should be evaluated by more sophisticated techniques, such as computed tomography (CT) scan or magnetic resonance imaging (MRI)

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

Confirmatory 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. Molecular testing may also be used to evaluate individuals with a single VHL-associated tumor and a negative family history of the disease. 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).

Predictive Testing: 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.

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)

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: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] * Codes	Description
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83904	Molecular diagnostics; mutation identification by sequencing, single segment,

	each segment
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation
83912	Molecular diagnostics; interpretation and report

HCPCS Codes	Description
S3842	Genetic testing for von hippel-lindau disease

ICD-9-CM Diagnosis Codes	Description
227.0	Benign neoplasm of adrenal gland
753.11	Congenital single renal cyst
759.6	Other congenital hamartoses, not elsewhere classified
V18.9	Family history of genetic disease carrier
V84.89	Genetic susceptibility to other disease

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	4/15/2007	0334	Genetic Testing for von Hippel-Lindau Disease

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