



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 Retinoblastoma

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Hyperlink to Related Coverage Policies

- Genetic Counseling
- Genetic Testing of Heritable Disorders
- Preimplantation Genetic Diagnosis
- Stem-Cell Transplantation for Solid Tumors in Children
- Transpupillary Thermal Therapy (TTT)

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. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers genetic testing for retinoblastoma as medically necessary for ANY of the following indications:

- confirmatory testing for an individual with unilateral or bilateral retinoblastoma
- predictive testing when the individual has a first- or second-degree relative* with a disease-causing mutation of gene RB1
- prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when the disease-causing mutation of gene RB1 has been identified in one or both parents

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes. First-degree relatives include 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.

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

CIGNA does not cover genetic testing for the susceptibility to retinoblastoma mutations in the general population because such screening is considered not medically necessary or of unproven benefit.

General Background

Retinoblastoma is a rare childhood cancer. It is a malignant tumor of the developing retina that usually occurs before the age of five years. Retinoblastoma affects an estimated four in one million children and accounts for approximately 3% of all cancers in children younger than 15 years of age (National Cancer Institute [NCI], 2010a). While it is a rare form of childhood cancer, it is the most common intraocular malignant neoplasm in children (Castillo and Kaufman, 2003).

In nearly 60% of retinoblastoma cases, the presenting sign is a reflection of light off a tumor behind the lens of the eye that results in the pupil appearing white (National Organization of Rare Disorders [NORD], 2008). Additional symptoms may include crossed eyes, differences in pupil size, decreased vision and, potentially, blindness in the affected eye. The clinical diagnosis of retinoblastoma is usually established by examining the fundus of the eye, using indirect ophthalmoscopy. Imaging studies can be used to support the diagnosis and stage of the tumor.

The type of treatment required for retinoblastoma depends on both the extent of the disease within the eye and whether the disease has spread beyond the eye, either to the brain or to the rest of the body. The goals of therapy include: eradicate the disease, preserve as much vision as possible, and decrease risk of late effects from treatment (NCI, 2010a). The treatment may include surgery to remove the eye, radiation therapy, cryotherapy, laser therapy (e.g., transpupillary thermotherapy, photocoagulation), chemotherapy, and chemoreduction, an approach to treatment that is often used in children with bilateral disease in the hope of avoiding enucleation and preserving vision in at least one eye. Management includes surveillance of affected individuals for early detection of second ocular and nonocular tumors. If retinoblastoma metastasizes, it can spread to the lymph nodes, bones or bone marrow; in rare cases, it can involve the central nervous system. Early diagnosis and treatment is of primary importance to the survival of patients with retinoblastoma. Those with hereditary retinoblastoma are at increased risk of developing other types of cancer in later life. In particular, children with hereditary retinoblastoma may also be at risk of developing a rare condition called trilateral retinoblastoma, which is retinoblastoma associated with an intracranial neuroblastic tumor (NCI, 2010a).

Retinoblastoma occurs as germline disease in approximately 40% of cases and as sporadic in approximately 60% (NCI, 2010a). Germline disease includes those patients with a positive family history (e.g., hereditary disease) and those patients who have sustained a new germline mutation at the time of conception. The germline form of retinoblastoma may manifest as unilateral or bilateral disease. Most unilateral disease is sporadic (e.g., non-familial, or nongermline), whereas all children with bilateral disease have the germline form. However, approximately 10–15% of children with unilateral sporadic retinoblastoma have a germline mutation (Shields and Shields, 2004). Unilateral tumors in infants are more likely to have germline mutations, whereas older children with unilateral tumors are more likely to have sporadic tumors. Genetic testing may assist in identifying those patients with a germline mutation.

Retinoblastoma results from a mutation in the gene RB1, which is a tumor suppressor gene located at chromosome 13q14. This is the only gene known to be associated with retinoblastoma. Predisposition to retinoblastoma is caused by mutations in the RB1 gene and is transmitted in an autosomal dominant manner. The risks to family members are dependent upon whether or not the proband has a germline RB1 mutation. The probability of detecting an RB1 gene mutation in an affected case depends on whether the tumor is unifocal or multifocal, whether the family history is positive or negative, and the sensitivity of the testing methodology.

In patients with more than one affected family member or bilateral retinoblastoma, molecular genetic testing is first performed on peripheral blood DNA. Almost all of these patients have a detectable mutation. In patients with bilateral retinoblastoma and no family history, an oncogenic mutation may not be identified in peripheral blood. In such cases, tumor DNA should be investigated. In situations where the tumor DNA demonstrates two mutations, or identifies one sequence alteration of the promotion region plus loss of heterozygosity, then the patient's peripheral blood can be tested for the presence of one of the mutations identified by tumor analysis. In

the situation where neither of the two mutations identified in the tumor is detected in the DNA from peripheral blood, then a mutational mosaicism is generally assumed (Lohmann and Gallie, 2000; updated 2010).

In individuals with unilateral retinoblastoma and no family history, molecular genetic testing is first performed on tumor tissue with the goal of identifying the two mutations that caused inactivation of both RB1 alleles. Molecular genetic testing for the presence of one of the two mutations identified in the tumor is then performed on the peripheral blood DNA. It is estimated that in about 15% of individuals with unilateral retinoblastoma, no family history of retinoblastoma, and one of the RB1 mutations identified in the tumor, the mutations are also detected in peripheral blood. This may be either a heterozygous mutation (i.e., indicates presence of germline mutation) or in a mosaic state (i.e., indicates presence of somatic mutation) (Lohmann and Gallie, 2000; updated 2010).

Molecular genetic testing may be used for confirmatory testing, predisposition testing, prenatal testing and preimplantation genetic diagnosis. In at-risk individuals, early recognition of retinoblastoma may allow for timely intervention and improved final outcome. Genetic counseling is required to identify relatives at increased risk. If relatives at risk are in early childhood (age five or under), repeated eye examinations under anesthesia are required. The primary goal of molecular testing is to exclude those at increased risk at a level of certainty that justifies deferring the eye examinations. Individuals who warrant surveillance for early manifestations of retinoblastoma include: individuals with retinomas and asymptomatic at-risk children. Use of DNA-based testing for early identification of at-risk family members improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited the disease-causing mutation (Lohmann and Gallie, 2000; updated 2010).

Prenatal Testing and Preimplantation Genetic Diagnosis (PGD)

The optimal time for determination of genetic risk, discussion of availability of prenatal testing and decisions about testing is before pregnancy. The disease-causing allele of an affected family member must be identified or the linkage established in the family before prenatal testing is performed. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by chorionic villus sampling (CVS) or by amniocentesis. Ultrasound examination may be used to identify ocular tumors in the event that disease-causing RB1 mutation is identified in the fetus (Lohmann and Gallie, 2000; updated 2010).

Preimplantation genetic diagnosis (PGD) refers to genetic testing of an early embryo resulting from in vitro fertilization. The testing is performed before implantation. PGD has recently been used as an alternative to prenatal testing with amniocentesis or chorionic villus sampling (CVS) techniques for detecting single gene disorders in embryos that have been identified as being at high risk for inheriting the gene disorder. PGD is available for families when a disease-causing mutation of gene RB1 has been identified in one or both parents.

Professional Societies/Organizations

American Society of Clinical Oncology: 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. The ASCO policy 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. In situations 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. In the absence of increased risk of a childhood malignancy, it is recommended to delay genetic testing until an individual is of sufficient age to make an informed decision regarding such tests (ASCO, 2003/ Robson, et al., 2010)

Summary

Retinoblastoma results from a mutation in the gene RB1, which is the only gene known to be associated with retinoblastoma. Genetic molecular testing will assist in determination of those who are at increased risk. In at-

risk individuals, early recognition of retinoblastoma may allow for timely intervention and improved final outcome.

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)
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83898	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern), each nucleic acid preparation
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
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
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)

HCPCS Codes	Description
S3841	Genetic testing for retinoblastoma

ICD-9-CM Diagnosis Codes	Description
190.5	Malignant neoplasm of retina
V19.1	Family history of other conditions; Other eye disorders
V84.09	Genetic susceptibility to other malignant neoplasm

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
V80.2	Special screening for neurological, eye, and ear diseases; other eye conditions
V82.71	Screening for genetic disease carrier status
	All other codes

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

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	11/15/2008	0223	Genetic Testing for Retinoblastoma

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