Cigna Medical Coverage Policy

Subject: Genetic Testing for Retinoblastoma

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain standard Cigna benefit plans. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, 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 supersedes 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 ©2013 Cigna

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 confirmatory (diagnostic) genetic testing for retinoblastoma (gene RB1) with sequence analysis or mutation scanning as medically necessary for BOTH of the following indications:

- germline DNA testing (e.g., peripheral blood, saliva) for EITHER of the following:
  - bilateral retinoblastoma
  - unilateral retinoblastoma and a first-, second-, or third-degree relative* with history of retinoblastoma

- testing of retinoblastoma tumor tissue for EITHER of the following:
  - unilateral retinoblastoma and no first-, second-, or third-degree relative* with a history of retinoblastoma
  - bilateral retinoblastoma with BOTH of the following:
    - no family history of retinoblastoma
    - a mutation has not been detected in the blood

Cigna covers genetic testing for retinoblastoma for a known familial mutation (i.e., testing for the known familial variant) as medically necessary for EITHER of the following:
• predictive testing in an individual with a blood 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

Cigna covers genetic testing for retinoblastoma as medically necessary using ANY of the following genetic testing methods when sequence analysis is negative and clinical suspicion of retinoblastoma remains high:

• deletion/duplication analysis
• targeted mutation analysis
• methylation analysis

*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.
*A third-degree relative is defined as a blood relative with whom an individual shares approximately 12.5% of his/her genes, including the individual's great-grandparents, great-aunts/uncles, and first cousins.

An individual undergoing genetic testing for retinoblastoma should have both pre- and post-test genetic counseling with a board-certified or board-eligible medical geneticist or a 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.

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**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], 2013a). 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, 2013a). 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, 2013a).

Retinoblastoma occurs in heritable or germline (25%) and nonheritable or sporadic (75%) forms (NCI, 2012a). 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 2013).

In individuals with unilateral retinoblastoma and no family history, molecular genetic testing may first be 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 2013).

Molecular genetic testing may be used for confirmatory testing, predictive 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 2013).

Molecular genetic testing for retinoblastoma includes (Lohmann and Gallie, 2000; updated 2013):

- Sequence analysis/mutation scanning is used to identify small deletions, insertions, and base substitutions in exons and splice site consensus regions which account for about 70% of oncogenic RB1 mutations (Lohmann and Gallie, 2000; updated 2010). Mutation scanning is a process by which a segment of DNA is screened by way of a variety of methods to identify variant gene region(s). The variant regions are further analyzed to identify the sequence alteration.
- When sequence analysis or mutation scanning is negative, further testing may be performed to detect a mutation. These testing methods include:
  - Deletion/duplication analysis that may be performed with these methodologies:
    - Fluorescent in situ hybridization (FISH): Deletions of all or parts of the RB1 gene have been identified by FISH analysis using probes derived from sequences of the RB1 gene.
    - Multiplex ligation-dependent probe amplification (MLPA): quantitative multiplex PCR with high-resolution fragment length analysis, and other methods are used to identify
submicroscopic whole-exon and multiexon deletions, insertions, and rearrangements, which account for about 16% of oncogenic RB1 mutations.

- Targeted mutation analysis: Recurrent CpG transitions at 11 CGA codons that result in nonsense mutations account for about 25% of oncogenic RB1 alterations and can be detected by mutation-specific detection methods. These methods are particularly useful for detecting mosaic recurrent mutations in blood and can detect mutant DNA levels that are below the limit of conventional sequence analysis. Low levels of mutational mosaicism have been identified in bilateral probands and in unilateral patients with affected children who inherited the mutation and, therefore, are clinically relevant.

- Methylation analysis: Hypermethylation of the RB1 gene promoter, which results in silencing gene expression, is observed in about 10%-12% of tumors from individuals with sporadic, unilateral retinoblastoma. In these individuals, analysis of the promoter methylation status in DNA from tumor is needed to identify the two inactive RB1 alleles that triggered tumor development.

Genetic Counseling
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. The genetic counseling should be provided by an independent specialty-trained genetics professional such as a medical geneticist or a genetic counselor who is an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counseling professional who is unaffiliated with the genetic testing lab performing the test(s).

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 2013).

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): 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)

National Society of Genetic Counselors (NSGC): NSGC published recommendations for the essential elements of genetic cancer risk assessment, counseling, and testing. The guidelines include (Riley, et al., 2012): Genetic testing should be offered when the following conditions apply:
• 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
The Canadian Retinoblastoma Society published the National Retinoblastoma Strategy Canadian Guidelines for Care. The guidelines include recommendations genetic testing and counseling for retinoblastoma (Rb) (Canadian Retinoblastoma Society, 2009):

Genetic testing:
- RB1 gene mutation identification testing for the first affected person (proband) in each Rb family (Level 2*)
- any tumor removed from a Rb patient be stored in a form appropriate for DNA studies (Level 2*)
- For bilaterally affected and familial unilateral probands, recommend that blood be studied, aided by tumor tissue as required (Level 2*)
- For unilateral, nonfamilial probands, it is recommended that tumor be studied first. If no tumor is available, recommend that blood be studied (Level 2*)
- When chromosome 13q14 deletion is discovered, recommend any genetic test report suggesting deletion or rearrangement of chromosome 13q14 in a child or adult trigger an urgent referral to ophthalmology within 48–72 hours (Level 2*)
- When the family RB1 mutation is known:
  - recommend genetic testing for all at-risk relatives (Level 2*)
  - recommend frequent clinical surveillance to detect Rb in children who carry the RB1 mutant allele of their family (Level 2*)
  - recommend awareness counseling about cancer in adult relatives who carry the RB1 mutant allele of their family (Level 2*)
  - recommend that surveillance for relatives not at risk be discontinued (Level 2*)
  - recommend early prenatal counseling, including a discussion of the advantages and disadvantages of invasive prenatal testing to support informed family planning decisions, and perinatal management of affected babies to facilitate the earliest possible treatment of tumors (Level 2*)
- when the family RB1 mutation is not known:
  - With a positive family history but no knowledge of the RB1 mutation, recommend that each at-risk family member be screened until age seven years, according to the empiric risk of developing Rb (Level 2*)

Genetic counseling:
- recommend genetic counseling for patients, parents and other relatives to discuss Rb, the risk and hereditary pattern of Rb, pregnancy options, post-delivery screening protocols and treatment options (Level 3*)
- recommend genetic counseling to explain the benefits and process of molecular analysis of the proband’s RB1 genes (Level 3*)
- recommend that the details and impact of the RB1 mutant allele be explained to the affected children and the family soon after the testing is complete; the clinical geneticist can counsel on the risks and therefore the intensity of recommended surveillance of children at risk to develop Rb (Level 3*)
- recommend that children with RB1 mutant alleles be offered repeated genetic counseling as they grow up, so that they completely understand their options and appropriate care (Consensus*)

*Level 1: Randomized controlled trials (RCTs) (or meta-analyses) without important limitations
Level 2: RCTs (or meta-analyses) with important limitations, Observational studies (non-RCTs or cohort studies) with overwhelming evidence
Level 3: Other observational studies (prospective cohort studies, case-control studies, case series)
Consensus: Inadequate or no data in population of interest, anecdotal evidence or clinical experience, 100% agreement of Steering & Expert Committee members

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: 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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References


