



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 Hemoglobinopathies

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Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	5
References	6
Policy History	8

Hyperlink to Related Coverage Policies

Genetic Counseling
 Genetic Disease Screening Panels
 Genetic Testing of Heritable Disorders
 Preimplantation Genetic Diagnosis
 Stem-Cell Transplantation for Sickle Cell Disease and Thalassemia Major

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Coverage Policy

CIGNA covers genetic testing for hemoglobinopathies (i.e., thalassemias and sickle cell disease) as medically necessary for ANY of the following indications:

- Confirmation of a diagnosis in EITHER of the following situations
 - symptomatic individual with clinical features suggestive of a hemoglobinopathy, results of testing by conventional studies (e.g., electrophoresis, liquid chromatography, or isoelectric focusing) yield equivocal results, and a definitive diagnosis remains uncertain
 - infant with a newborn screening test positive for a hemoglobinopathy
- Preconception or prenatal genetic testing to determine carrier status of a prospective biologic parent with the capacity and desire to reproduce when ANY of the following applies:
 - an affected family member (first- or second-degree relative*) who has thalassemia or sickle cell disease
 - the individual is the reproductive partner of a known carrier (disease-causing mutation of gene HBB, HBA1, or HBA2) and the couple has the capacity and intention to reproduce
 - the individual is of African, Southeast Asian, or Mediterranean descent
- Prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) in EITHER of the following situations:

- both parents are known carriers of the disorder or have a family history (first- or second-degree relative*) of the disorder
- one parent is a known carrier and the mutation status of the other parent is not known and can't be determined

*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.

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 hemoglobinopathies in the general population because such screening is considered not medically necessary or of unproven benefit.

General Background

Hemoglobinopathies are inherited single gene disorders that affect hemoglobin production and function. Hemoglobinopathies can be classified broadly as disorders that result from structurally altered hemoglobin molecules or that arise from numerical imbalance of otherwise normal globin chain synthesis. The major classes of hemoglobinopathies include sickle cell disease and the thalassemias. In addition to the major classes, there are also over 700 hemoglobin variants that have been detected. While most of these are rare, the most clinically significant are Hb S, Hb C, Hb E, Hb D-Punjab and Hb O-Arab (Old, 2003). Initially, the abnormal hemoglobins were assigned letters in alphabetical order; however, it was found that this system would not provide sufficient designations. In 1960, the system of nomenclature was revised, and letters R and T through Z were not assigned. The new system utilized a solitary letter designation for normal hemoglobins A and F and for the abnormal hemoglobins C, E, S and H. The letters may also be used as part of a more complete common name. The abnormal hemoglobins are now assigned both a common name and scientific designation. The common name is selected by the discoverer and usually represents a geographic area (Greer, et al., 2009).

The inheritance pattern of hemoglobinopathies is autosomal recessive. These conditions are passed on to children by parents who carry mutated globin gene mutations. A child who inherits two trait genes, one from each parent who is a carrier, will have the disease. A child of two carriers has a 25% chance of receiving two trait genes and developing the disease, a 50% chance of being a thalassemia trait carrier, and a 25% chance of being unaffected. In the situation where one parent is a carrier, there is a 50% chance of a child being a carrier. In a situation where one parent is a carrier and one parent is affected, then there is a 50% chance of the individual being a carrier and 50% chance of being affected. In addition, it is possible for co-inheritance of alpha and beta globin gene mutations to occur. In these situations, an individual may inherit a different abnormal mutant allele from each parent and exhibit composite features of each—for example, patients inheriting sickle beta thalassemia exhibit features of both beta thalassemia and sickle cell anemia.

Diagnosis is best established by recognition of a characteristic history, physical findings, peripheral blood smear morphology, and abnormalities of the complete blood cell count. Laboratory evaluation identifies the specific hemoglobinopathy suspected clinically. The laboratory diagnostic testing for hemoglobinopathies may include high performance liquid chromatography (HPLC), isoelectric focusing (IEF), cellulose acetate and citrate agar electrophoresis.

Thalassemia

Thalassemia is an autosomal recessive, genetic blood disorder that affects a patient's ability to produce hemoglobin, resulting in anemia. The condition is prevalent in people of Mediterranean, Middle Eastern and Southeast Asian ancestry. There are two main types of thalassemia disease: alpha and beta thalassemia. Alpha thalassemia includes disorders of the alpha hemoglobin chain, while the beta thalassemia affects the beta hemoglobin chain.

Alpha Thalassemia: Alpha thalassemia will occur when one or more of the four alpha chain genes fail to function. With this disorder, the failed genes are almost invariably lost from the cell. The genes that are most commonly associated with alpha thalassemia are HBA1 and HBA2. The severity of this condition is dependent on the extent of the alpha globin chain defect. There are two carrier states of alpha thalassemia (Galanello, et al., 2008):

- The loss of only one gene will result in a carrier, often referred to as a silent carrier. It is characterized by either a silent hematologic phenotype or a moderate thalassemia-like picture.
- The loss of two genes produces a condition with small red blood cells and, at most, a mild anemia. The condition can be detected by routine blood testing.

There are two clinically significant forms of alpha thalassemia (Galanello, et al., 2008):

- Hemoglobin H (HbH) disease: This form results from the loss of three alpha genes. It will produce a serious hematological condition, and patients will have significant anemia. This form is characterized by microcytic hypochromic hemolytic anemia, hepatosplenomegaly, mild jaundice and sometimes thalassemia-like bone changes. Occasional red blood cell transfusions may be needed during hemolytic or aplastic crises. Transfusions are indicated for severe anemia affecting cardiac function and erythroid expansion that result in severe bone changes and extramedullary erythropoiesis. Splenectomy may be performed in case of massive splenomegaly or hypersplenism.
- Hb Bart hydrops fetalis syndrome: This is the most severe form, and results from all four of the alpha globin alleles being deleted or dysfunctional. It is characterized by fetal onset of generalized edema, pleural and pericardial effusions and severe hypochromic anemia, in the absence of ABO or Rh blood group incompatibility. This condition usually results in death in the neonatal period.

Molecular genetic testing is available in clinical laboratories and may be used for diagnostic testing, carrier testing, prenatal diagnosis and prediction of clinical severity. The clinical methods of molecular genetic testing include (Galanello, et al., 2008):

- Targeted mutation analysis: Polymerase chain reaction (PCR)-based methods may be used to detect deletions of the gene HBA1 and HBA2.
- Sequence analysis: When a deletion mutation is not identified and there is high suspicion for alpha thalassemia, then sequence analysis can be used to identify point mutations, or sequence variation, in the coding of HBA1 and HBA2.

Beta Thalassemias: Beta thalassemia is characterized by a reduced synthesis of the hemoglobin beta chain that results in microcytic hypochromic anemia, abnormal peripheral blood smear with nucleated red blood cells and reduced amounts of hemoglobin A (HbA) on hemoglobin analysis. Patients with thalassemia major have severe anemia and hepatosplenomegaly. The disease will be noticed in the first two years of life. Treatment includes a regular transfusion program and chelation therapy, with the aim of reducing transfusion iron overload. Thalassemia major may also be referred to as Cooley's anemia. Patients with thalassemia intermedia present later in life and usually have milder anemia that only rarely requires transfusion. A carrier is often referred to as having thalassemia minor (Cao and Galanello, 2010).

Molecular genetic testing of the gene encoding the globin beta chain (gene HBB) is available in clinical laboratories. Genetic testing may be useful for prediction of the clinical phenotype in some cases as well as presymptomatic diagnosis of at-risk family members and prenatal diagnosis. The gene HBB is the gene most commonly known to be associated with beta-thalassemia. Molecular genetic counseling may be used to identify disease-causing point mutations in the gene encoding the hemoglobin beta chain (gene HBB), carrier testing, prenatal diagnosis and prognosis. Clinical methods used in genetic testing of beta thalassemia include (Cao and Galanello, 2010):

- Targeted mutation analysis: The beta thalassemias may be caused by more than 200 HBB gene mutations. However, it is noted that the prevalent molecular defects are limited in each at-risk population. The commonly occurring mutations of the HBB gene are detected by a number of PCR-

based procedures. The sensitivity of this method is variable depending on mutations included in the panel and the individual's ethnicity.

- Mutation scanning/sequence analysis: This testing method may be used when targeted mutation analysis fails to detect mutation. Sensitivity of both mutation scanning and sequence analysis is 99%.

Sickle Cell Disease

The term sickle cell disease encompasses a group of symptomatic disorders associated with mutations in the HBB gene and defined by the presence of hemoglobin S (Hb S). The disorders are found primarily in people of African, Mediterranean and Southeast Asian ancestry. The condition is characterized by variable degrees of hemolysis and intermittent episodes of vascular occlusion, resulting in tissue ischemia and acute and chronic organ dysfunction. The consequences of hemolysis include chronic anemia, jaundice, predisposition to aplastic crisis, cholelithiasis and delayed growth and sexual maturation. The condition can result in acute and chronic injury to most of the organs, in particular, the spleen, brain, lungs and kidneys (Bender, 2006). Sickle cell anemia (Hb SS) accounts for 60–70% of sickle cell disease in the United States. Other forms result from co-inheritance of Hb S with other abnormal globin beta chain variants. The most common of these forms includes: sickle-hemoglobin C disease (Hb SC) and two types of sickle beta-thalassemia (Bender, 2006). Sickle cell trait refers to situations where the individual is a sickle cell carrier and is asymptomatic.

Newborn screening tests now identify most infants with sickle cell disease born in the United States. An infant diagnosed with hemoglobins that suggest sickle cell disease or other clinically significant hemoglobinopathies requires confirmatory testing of a separate blood sample by six weeks of age. Specimens with abnormal screening results are retested using a second, complementary HPLC technique or deoxyribonucleic acid (DNA)-based assay. Newborns affected by sickle cell disease benefit from early detection, as prophylactic penicillin therapy can then be instituted early to prevent the pneumococcal sepsis to which their impaired splenic function predisposes them. Regardless of the outcome of testing in a newborn, it is recommended that additional testing be performed at one year of age. This testing includes complete blood count (CBC), reticulocyte count, some form of electrophoresis or HPLC, a measure of iron status and inclusion body preparation. This will assist in assessment of co-existing alpha or beta thalassemia syndromes. If one parent has sickle cell trait and the other has beta-thalassemia trait, there is still a 25% possibility with each pregnancy that there will be a significant hemoglobinopathy (Bender, 2006).

The treatment for sickle cell disease includes oral hydration and oral analgesics, including opiates, acetaminophen and ibuprofen for uncomplicated episodes of vaso-occlusive pain. Transfusions may also be used for situations of cardiovascular instability. Splenectomy may be required for multiple or severe episodes of splenic sequestration (Bender, 2006). Stem cell transplantation has been used recently, with pediatric patients in particular. Stem cell transplantation from a matched donor may be curative in individuals with sickle cell disease. The risks and morbidity associated with this procedure have limited its use to a select group of individuals with significant complications (Bender, 2006).

Clinical uses of molecular genetic testing for sickle cell disease include confirmatory testing, carrier testing and prenatal diagnosis. The available molecular genetic testing methods for sickle cell disease include targeted mutation analysis and sequence analysis.

Prenatal DNA Testing

The optimal time for determination of genetic risk, determination of carrier status and education regarding the availability of prenatal testing is before pregnancy. Prenatal diagnosis for pregnancies at risk is possible by analysis of the DNA extracted from fetal cells obtained by amniocentesis (performed at approximately 15–18 weeks gestation) or chorionic villus sampling (CVS) (performed at approximately 10–12 weeks gestation). It is important to note that both disease-causing HBB alleles of the carrier parents must be identified before prenatal testing can be performed. In situations where the mother is a known carrier and the father is unknown and/or unavailable for testing, options should be explored in the context of formal genetic counseling. Polymerase chain reaction (PCR)-based methods of DNA analysis are used primarily to assess fetal DNA mutations. These PCR tests include techniques such as sequence analysis and mutation analysis (Bender, 2006; Cao and Galanello, 2010).

Preimplantation Genetic Diagnosis (PGD)

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 and CVS techniques for detecting single gene disorders in embryos that have been identified as at high risk for inheriting the gene disorder. PGD may be available for families in which the disease-causing mutations have been identified in an affected family member (Bender, 2006).

Professional Societies/Organizations

American College of Obstetricians and Gynecologists (ACOG): The ACOG clinical management guidelines for hemoglobinopathies in pregnancies include the following recommendations (ACOG, 2007):

- Individuals of African, Southeast Asian, and Mediterranean descent are at increased risk for being carriers of hemoglobinopathies and should be offered carrier screening and, if both parents are determined to be carriers, genetic counseling.
- A complete blood count and hemoglobin electrophoresis are appropriate laboratory tests for screening for hemoglobinopathies. Solubility tests alone are inadequate for screening because they fail to identify important transmissible hemoglobin gene abnormalities affecting fetal outcome.
- Couples at risk for having a child with sickle cell disease or thalassemia should be offered genetic counseling to review prenatal testing and reproduction options. Prenatal diagnosis of hemoglobinopathies is best accomplished by DNA analysis of cultured amniocytes or chorionic villi.

Summary

Hemoglobinopathies can be classified broadly as single gene disorders that result from structurally altered hemoglobin molecules or that arise from numerical imbalance of otherwise normal globin chain synthesis. Sickle cell disease and thalassemia (alpha and beta) are among the major classes of the hemoglobinopathies. Clinical indications for molecular genetic testing for hemoglobinopathies include confirmation of diagnosis, preconception or prenatal genetic testing of a prospective biologic parent to determine carrier status, prenatal testing of a fetus and preimplantation genetic diagnosis of an embryo.

Coding/Billing Information

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

Covered when medically necessary:

CPT [®] * Codes	Description
83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
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
83893	Molecular diagnostics; dot/slot blot production, each nucleic acid preparation
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern), each nucleic acid preparation
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
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)
83902	Molecular diagnostics; reverse transcription
83903	Molecular diagnostics; mutation scanning, by physical properties (eg, single strand conformational polymorphisms [SSCP], heteroduplex, denaturing gradient gel electrophoresis [DGGE], RNA'ase A), single segment, each
83904	Molecular diagnostics; mutation identification by sequencing, single segment,

	each segment
83905	Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment
83906	Molecular diagnostics; mutation identification by allele specific translation, single segment, each segment
83907	Molecular diagnostics; lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue), each specimen
83908	Molecular diagnostics; amplification, signal, each nucleic acid sequence
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation
83912	Molecular diagnostics; interpretation and report
	Multiple/varied

HCPCS Codes	Description
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin E beta-thalassemia
S3850	Genetic testing for sickle cell anemia

ICD-9-CM Diagnosis Codes	Description
282.41-282.49	Thalassemias
282.5	Sickle cell trait
282.60-282.69	Sickle cell disease
282.7	Other hemoglobinopathies
V18.9	Family history of genetic disease carrier

*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	9/15/2008	0192	Genetic Testing for Hemoglobinopathies

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