Genetic Testing for Alpha Thalassemia

Description of Procedure or Service

Alpha thalassemia represents a group of clinical syndromes of varying severity characterized by hemolytic anemia and ineffective hematopoiesis. Genetic defects in any or all of four alpha globin genes are causative of these syndromes. The rate of variants in the alpha thalassemia gene varies across ethnic groups and is highest in individuals from Southeast Asia, Africa, and the Mediterranean region. This policy will evaluate genetic testing for confirming a diagnosis of alpha thalassemia and for preconception (carrier) testing. Prenatal (in utero) testing is not addressed in this policy.

Hemoglobin, which is the major oxygen carrying protein molecule of red blood cells, consists of two alpha globin chains and two beta globin chains. Alpha-thalassemia refers to a group of syndromes that arise from deficient production of alpha globin chains. Deficient alpha-globin production leads to an excess of beta-globin chains, which results in anemia by a number of mechanisms:

- Ineffective erythropoiesis in the bone marrow.
- Production of nonfunctional hemoglobin molecules.
- Shortened survival of red blood cells (RBCs) due to intravascular hemolysis and increased uptake of the abnormal RBCs by the liver and spleen.

The physiologic basis of alpha thalassemia is a genetic defect in the genes coding for alpha globin production. Each individual carries four genes that code for alpha globin, (2 copies each of HBA1 and HBA2, located on chromosome 16), with the wild genotype (normal) being aa/aa. Genetic variants may occur in any or all of these four alpha globin genes. The number of genetic variants determines the phenotype and severity of the alpha thalassemia syndromes. The different syndromes are classified as follows:

- **Silent carrier (alpha-thalassemia minima)**. This arises from one of four abnormal alpha genes (aa/a-), and is a silent carrier state. A small amount of abnormal hemoglobin can be detected in the peripheral blood, and there may be mild hypochromia and microcytosis present, but there is no anemia or other clinical manifestations.

- **Thalassemia trait (alpha-thalassemia minor)**. This is also called alpha-thalassemia trait, and arises from the loss of two alpha globin genes, resulting on one of two genotypes (aa/-, or a-/a-). There is a mild anemia present, and red blood cells are hypochromic and microcytic. Clinical symptoms are usually absent and in most cases the hemoglobin electrophoresis is normal.

- **Hemoglobin H disease – HbH (alpha-thalassemia intermedia)**. This syndrome results from three abnormal alpha globin genes (a-/a-), resulting in a moderate to severe anemia.
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In HbH disease, there is an imbalance in alpha and beta globin gene chain synthesis, resulting in the precipitation of excess beta chains into the characteristic hemoglobin H, or beta-tetramer. This condition has marked phenotypic variability, but the majority of individuals have mild disease and live a normal life without medical intervention.

A minority of individuals may develop clinical symptoms of chronic hemolytic anemia. These include neonatal jaundice, hepatosplenomegaly, hyperbilirubinemia, leg ulcers, and premature development of biliary tract disease. Splenomegaly can lead to the need for splenectomy, and transfusion support may be required by the third to fourth decade of life. It has been estimated that approximately 25% of patients with HbH disease will require transfusion support during their lifetime. In addition, increased iron deposition can lead to premature damage to the liver and heart. Inappropriate iron therapy and oxidant drugs should be avoided in patients with HbH disease.

There is an association between genotype and phenotype among patients with HbH disease. Individuals with a non-deletion variant typically have an earlier presentation, more severe anemia, jaundice, and bone changes, and more frequently require transfusions.

- **Hemoglobin Bart syndrome (alpha thalassemia major).** This syndrome results from variants in all four alpha globin genes (αα/αα), which prevents production of alpha globin chains. This condition causes hydrops fetalis, which often leads to intrauterine death, or death shortly after birth. There are also increased complications of pregnancy for an individual carrying a fetus with hydrops fetalis. These include hypertension, preeclampsia, antepartum hemorrhage, renal failure, premature labor, and abruption placenta.

Alpha thalassemia is a common genetic disorder, affecting approximately 5% of the world’s population. The frequency of variants is highly dependent upon ethnicity, with the highest rates in Asians, and much lower in Northern Europeans. The carrier rate is estimated to be 1 in 20 in Southeast Asians, 1 in 30 for Africans, and between 1 in 30 and 1 in 50 for individuals of Mediterranean ancestry. In contrast, for individuals of northern European ancestry, the carrier rate is less than 1 in 1000.

**Genetic testing**

A number of different types of genetic abnormalities are associated with alpha-thalassemia. More than one hundred different genetic variants have been described. Deletion of one or more of the alpha globin chains is the most common genetic defect. This is the type of genetic defect found in approximately 90% of cases. Large genetic rearrangements can also occur from defects in crossover and/or recombination of genetic material during reproduction. Point mutations in one or more of the alpha genes can occur that impair transcription and/or translation of the alpha globin chains.

Testing is commercially available through several genetic labs. Targeted variant analysis for known alpha-globin gene variants can be performed by polymerase chain reaction (PCR). PCR can also be used to identify large deletions or duplications. Newer testing methods have been developed to facilitate identification of alpha thalassemia variants, such as multiplex amplification methods and real-time PCR analysis. In patients with suspected alpha thalassemia and a negative PCR test for genetic deletions, direct sequence analysis of the alpha-globin locus is generally performed to detect point variants.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for alpha thalassemia is available.
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under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing for alpha thalassemia when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Alpha Thalassemia is covered

Preconception (carrier) testing for alpha thalassemia in prospective parents may be considered medically necessary when both parents have evidence of possible alpha thalassemia (including alpha thalassemia minor, hemoglobin H disease [alpha thalassemia intermedia], or alpha thalassemia major) based on biochemical testing.

When Genetic Testing for Alpha Thalassemia is not covered

Genetic testing for alpha thalassemia is considered not medically necessary when the above medical criteria are not met.

Genetic testing of patients with hemoglobin H disease (alpha-thalassemia intermedia) to determine prognosis is considered investigational.

Genetic testing to confirm a diagnosis of alpha thalassemia is considered not medically necessary.

Policy Guidelines

The evidence for individuals who have suspected alpha thalassemia who receive genetic testing for alpha-thalassemia includes case reports and case series documenting the association of pathogenic variants with the clinical syndromes. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and quality of life. For the alpha thalassemia syndromes that have clinical implications, the diagnosis can be made based on biochemical testing without the need for genetic testing. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

The evidence for individuals with hemoglobin H disease (alpha thalassemia intermedia) who receive genetic testing for alpha thalassemia includes cases series that correlate specific variants with prognosis of disease. Relevant outcomes are overall survival, disease-specific survival, symptoms, and quality of life. There is some evidence for a genotype-phenotype correlation with disease severity, but there is no current evidence to indicate that patient management or outcomes would be altered through genetic testing. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.
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The evidence for individuals who have biochemical evidence of alpha thalassemia who are considering conception (carrier) who receive genetic testing for alpha thalassemia includes case reports and case series that correlate pathogenic variants with clinical disease. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. Preconception (carrier) testing is intended to avoid the most serious form of alpha-thalassemia, hemoglobin Bart’s. This condition leads to intrauterine death or death shortly after birth and is associated with increased obstetrical risks for the mother. Screening of populations at risk is first done by biochemical tests, including hemoglobin electrophoresis and complete blood count (CBC) and peripheral smear, but these tests cannot reliably distinguish between the carrier and trait syndromes, and cannot determine which configuration of variants is present in alpha-thalassemia trait. They therefore cannot completely determine the risk of a pregnancy with hemoglobin Bart’s and hydrops fetalis. Genetic testing can determine with certainty the number of abnormal genes present, and therefore can more precisely determine the risk of hydrops fetalis. Therefore, the evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81257, 81404

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Specialty Matched Consultant Advisory Panel review 1/2014


Specialty Matched Consultant Advisory Panel review 8/2014

Medical Director review 8/2014

Specialty Matched Consultant Advisory Panel review 8/2015
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Medical Director review 8/2015


Medical Director review 7/2016


Medical Director review 2/2017

Specialty Matched Consultant Advisory Panel review 7/2017

Medical Director review 7/2017

Policy Implementation/Update Information

10/1/13 New Evidence Based Guideline developed. Preconception (carrier) testing for alpha thalassemia in prospective parents may be appropriate when both parents have evidence of alpha thalassemia based on biochemical testing. Genetic testing to confirm a diagnosis of alpha thalassemia is not recommended. Genetic testing for alpha thalassemia in other clinical situations (recognizing that prenatal testing is not addressed in this policy) is not recommended. Medical Director review 9/2013. (mco)


9/30/14 “When Recommended” statement revised to state: “Preconception (carrier) testing for alpha thalassemia in prospective parents may be appropriate when both parents have evidence of possible alpha thalassemia (including alpha thalassemia minor, hemoglobin H disease [alpha thalassemia intermedia], or alpha thalassemia major) based on biochemical testing.”. Description section updated. References updated. Specialty Matched Consultant Advisory Panel review 8/2014. Medical Director review 8/2014. (mco)


12/30/16 Minor revisions to description section. No change to policy statement/intent. (jd)

3/31/17 Minor revisions with updated genetic terminology. Medical Director review 2/2017. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational
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purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.