MEDICAL POLICY – 12.04.519
Genetic Testing for Alpha Thalassemia

BCBSA Ref. Policy: 2.04.104

Effective Date: May 1, 2017
Last Revised: April 11, 2017
Replaces: 12.04.104

RELATED MEDICAL POLICIES:
12.04.116  Invasive Prenatal (Fetal) Diagnostic Testing
12.04.305  Preimplantation Genetic Testing in Embryos
12.04.518  Carrier Testing for Genetic Diseases

Select a hyperlink below to be directed to that section.

POLICY CRITERIA  |  CODING  |  RELATED INFORMATION
EVIDENCE REVIEW  |  REFERENCES  |  HISTORY

∞  Clicking this icon returns you to the hyperlinks menu above.

Introduction

Thalassemia is an inherited blood disorder where hemoglobin and red blood cells are abnormal. Hemoglobin is an important protein in red blood cells that carries oxygen to tissues in the body. People with thalassemia have genes that result in hemoglobin that does not bind oxygen very well. There are several types of thalassemia, including alpha thalassemia and thalassemia intermedia. The type of thalassemia a person develops depends on how many mutations are inherited. Some babies show signs of thalassemia at birth. In other cases, signs develop during the first two years of childhood. People who inherit only one mutation won’t have any signs or symptoms of thalassemia but do carry the gene. This policy discusses genetic testing to confirm a thalassemia diagnosis or look at how the condition might progress. Testing of parents for alpha thalassemia is discussed in a separate policy (see Related Policies).

Note:  The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
Testing | Investigational
---|---
**Prognosis of alpha thalassemia intermedia** | Genetic testing to determine the prognosis of patients with hemoglobin H disease (alpha thalassemia intermedia) is considered investigational.

**Other clinical situations** | Genetic testing for alpha thalassemia in other clinical situations (recognizing that neither preconception carrier testing nor prenatal testing is addressed in this policy) is considered investigational.

Testing | Medical Necessity
---|---
**Diagnosis of alpha thalassemia** | Genetic testing to confirm a diagnosis of alpha thalassemia is considered **not medically necessary**.

Coding

<table>
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<th>CPT</th>
<th>Description</th>
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<td>81257</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)</td>
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<tr>
<td>81404</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia), duplication/deletion analysis</td>
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</table>

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**Related Information**

This policy does not address prenatal (in utero or preimplantation) genetic testing nor preconception carrier testing for α-thalassemia (see Related Policies).

The diagnosis of α-thalassemia is made by biochemical testing. Biochemical testing consists of complete blood count (CBC), microscopic examination of the peripheral smear, and Hg electrophoresis. In silent carriers and in α-thalassemia trait, the Hg electrophoresis will most
likely be normal. However, there should be evidence of possible α-thalassemia minor on the CBC and peripheral smear.

**Genetics Nomenclature Update**

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” to describe variants identified that cause Mendelian disorders.

**Table 1 Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
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</table>

**Table 2 ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>
Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Evidence Review

This evidence review was created in August 2013, with review a MEDLINE review of the literature through July 15, 2013, and was updated periodically with literature reviews. The most recent literature review covered the period through December 20, 2016.

The published literature on genetic testing for α-thalassemia consists primarily of reports describing the molecular genetics of testing, the types of variants encountered, and genotype-phenotype correlations.5,6,8-12

Description

Alpha-thalassemia represents a group of clinical syndromes of varying severity characterized by hemolytic anemia and ineffective formation of blood or blood cells (hematopoiesis). Genetic defects in any or all of 4 α-globin genes are causes of these syndromes. The rate of variants in the α-thalassemia gene varies across ethnic groups and is highest in individuals from Southeast Asia, Africa, and the Mediterranean region.
Background

Hemoglobin, is the major oxygen carrying protein molecule of red blood cells, consists of 2 alpha (α)-globin chains and 2 beta (β)-globin chains. Alpha-thalassemia refers to a group of syndromes that arise from deficient production of α-globin chains. Deficient α-globin production leads to an excess of β-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 RBCs [red blood cells] due to intravascular hemolysis and increased uptake of the abnormal RBCs by the liver and spleen

The physiologic basis of α-thalassemia is a genetic defect in the genes coding for α-globin production. Each individual carries four genes that code for α-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 4 α-globin genes. The number of genetic variants determines the phenotype and severity of the α-thalassemia syndromes. The different syndromes are classified as follows:

- **Silent carrier (α-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 (α-thalassemia minor):** This is also called α-thalassemia trait and arises from the loss of 2 α-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 Hg electrophoresis is normal.

- **Hemoglobin H disease (α-thalassemia intermedia):** This syndrome results from three abnormal α-globin genes (a-/a-), resulting in a moderate to severe anemia. In HgH disease, there is an imbalance in α- and β-globin gene chain synthesis, resulting in the precipitation of excess β chains into the characteristic hemoglobin H, or β-tetramer. This condition has marked phenotypic variability, but most 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 HgH disease will require transfusion support during their lifetime.\(^3\) 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 HgH disease. There is an association between genotype and phenotype among patients with HgH disease. Individuals with a nondeletion variants typically have an earlier presentation, more severe anemia, jaundice, and bone changes, and more frequently require transfusions.\(^4\)

- **Hemoglobin Bart syndrome (α-thalassemia major):** This syndrome results from variants in all 4 α-globin genes (\(-/-\)), resulting in absent production of α-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 a woman carrying a fetus with hydrops fetalis. These include hypertension, preeclampsia, antepartum hemorrhage, renal failure, premature labor, and abruption placenta.\(^3\)

### Epidemiology

Alpha-thalassemia is a common genetic disorder, affecting approximately 5% of the world’s population.\(^3\) The frequency of variants is highly dependent on ethnicity, with the highest rates seen in Asians, and much lower rates 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 1,000.

### Genetic Testing

A number of different types of genetic abnormalities are associated with α-thalassemia. More than one hundred different genetic variants have been described. Deletion of one or more of the α-globin chains is the most common genetic defect. This is the type of genetic defect found in approximately 90% of cases.\(^4,5\) Large genetic rearrangements can also occur from defects in crossover and/or recombination of genetic material during reproduction. Point variants in one or more of the α genes can occur that impair transcription and/or translation of the α-globin chains.

Testing is commercially available through several genetic labs. Targeted variant analysis for known α-globin gene variants can be performed by polymerase chain reaction (PCR).\(^4,5\) PCR can also be used to identify large deletions or duplications. Newer testing methods have been
developed to facilitate identification of α-thalassemia variants, such as multiplex amplification methods and real-time PCR analysis. In patients with suspected α-thalassemia and a negative PCR test for genetic deletions, direct sequence analysis of the α-globin locus is generally performed to detect point variants.

Genetic Testing For Alpha-Thalassemia

Analytic Validity

A variety of testing methods can be used to evaluate the 2 genes related to α-globin production, HBA1 and HBA2, including sequence analysis of the entire coding region, targeted variant analysis via polymerase chain reaction (PCR), and deletion/duplication analysis. Therefore, the analytic validity depends on the method used, but would generally be expected to be high.

One 2016 study identified evaluated the reproducibility and accuracy of a PCR-based multicolor melting curve analysis method for detecting common nondeletional variants in the HBA2 gene from 700 whole blood samples. Reproducibility of the assay was high. In the clinical samples, there was 100% concordance between the 20 genotypes identified and the genotyping method. Petropoulou et al (2015) evaluated a PCR-based high-resolution melting curve analysis of duplicated areas of the HBA1 and HBA2 genes with novel nondeletion variants. The study included 62 samples with previously identified novel variants and 18 normal controls; the melting curve analysis was able to distinguish at least 80% of novel homozygote samples detected by earlier generation tests.

Clinical Validity

Clinical validity is expected to be high when the causative variant is a large deletion of 1 or more α-globin gene, as PCR testing is generally considered highly accurate for this purpose. When a point variant is present, the clinical validity is less certain.

In 2016, Henderson et al reported on a retrospective study of genotype and phenotype correlations of the novel thalassemia and abnormal hemoglobin variants identified after adoption of routine DNA sequencing of α- and β-globin genes for all U.K. samples referred for evaluation of hemoglobinopathy for the preceding 10 years. Of a total of approximately 12,000 samples, 15 novel α⁺-thal variants, 19 novel β-thal variants, and 11 novel β-globin variants were detected.
Clinical Utility

There are several potential areas for clinical utility. Genetic testing can be used to determine the genetic abnormalities underlying a clinical diagnosis of α-thalassemia. It can also be used to define the genetics of α-globin genes in relatives of patients with a clinical diagnosis of α-thalassemia. Preconception (carrier) testing can be performed to determine the likelihood of an offspring with an α-thalassemia syndrome. Prenatal (in utero) testing can also be performed to determine the presence and type of α-thalassemia of a fetus. Neither preconception (carrier) testing nor prenatal testing are addressed in this evidence review.

Confirmation of Diagnosis

The diagnosis of α-thalassemia can be made without use of genetic testing. This is first done by analysis of the complete blood count (CBC) and peripheral blood smear, in conjunction with testing for other forms of anemia. Patients with a CBC demonstrating microcytic, hypochromic red blood cell (RBC) indices who are not found to have iron deficiency, have a high likelihood of thalassemia. On peripheral blood smear, the presence of inclusion bodies and target cells is consistent with the diagnosis of α-thalassemia.

Hemoglobin electrophoresis can distinguish between the asymptomatic carrier states and α-thalassemia intermedia (HbH disease) by identifying the types and amounts of abnormal hemoglobin present. In the carrier states, greater than 95% of the Hb molecules are normal (HbA) with a small minority of HgBA2 present (1%-3%). Alpha thalassemia intermedia is diagnosed by finding a substantial portion of HgH (1%-30%) on electrophoresis. In α-thalassemia major, the majority of the Hg is abnormal, in the form of hemoglobin Bart (85%-90%).

However, biochemical testing, including CBC and hemoglobin electrophoresis, cannot always reliably distinguish between the asymptomatic carrier state and α-thalassemia trait, as the hemoglobin electrophoresis is typically normal in both conditions. Genetic testing can differentiate between the asymptomatic carrier state (α-thalassemia minima) and α-thalassemia trait (α-thalassemia minor) by elucidating the number of abnormal genes present. This distinction is not important clinically because both the carrier state and α-thalassemia trait are asymptomatic conditions that do not require specific medical care treatment. Alpha-thalassemia trait may have overlap in RBC indices values with iron deficiency states, so it is important that iron supplementation not be continued unnecessarily in patients with α-
thalassemia trait. However, it would be reasonable to make a diagnosis of α-thalassemia trait in a patient with microcytic, hypochromic RBC indices without evidence of iron deficiency, either before or after a trial of iron supplementation. Because the diagnosis of clinically relevant α-thalassemia conditions can usually be made without genetic testing, there is little utility to genetic testing of a patient with a clinical diagnosis of thalassemia to determine the underlying genetic abnormalities.

**Prognostic Testing in Patients With HbH Disease**

Among patients with hemoglobin H disease, there is heterogeneity in the nature of the variant (i.e., deletional vs nondeletional), with variations across geographic areas and ethnic groups. Patients with deletional variants may have a less severe course of illness than those with nondeletional variants. In a cohort of 147 Thai pediatric patients with HbH disease, those with nondeletional variants were more likely to have pallor after fever, hepatomegaly, splenomegaly, jaundice, short stature, need for transfusions, and gallstones. The evidence suggests that different genetic variants leading to α-thalassemia are associated with differences in prognosis. New treatments for some of the complications of HbH disease that result from ineffective erythropoiesis and iron overload and may differ for different genotypes are under development. However, no evidence was identified to indicate that patient management or outcomes would be changed by prognostic testing.

**Section Summary: Clinical Utility of Genetic Testing**

The clinical utility of genetic testing for α-thalassemia may occur in several settings. For confirming a diagnosis of α-thalassemia, because the diagnosis can generally be made on the basis of nongenetic testing, there is little utility to genetic testing. For patients with hemoglobin H disease, there may be a genotype-phenotype correlation for disease severity; however, no studies were identified that suggested that patient management or outcomes would be altered by genetic testing; therefore, genetic testing for determining the prognosis of hemoglobin H (HbH) disease is not associated with improved clinical utility.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in January 2017 did not identify any ongoing or unpublished trials that would likely influence this review.
Summary of Evidence

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

For individuals who have hemoglobin H disease (α-thalassemia intermedia) who receive genetic testing for α-thalassemia, the evidence includes case 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 no current evidence indicates that patient management or outcomes would be altered by genetic testing. The evidence is insufficient to determine the effects of the technology on health outcomes.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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 Improvement Act (CLIA). Genetic testing for α-thalassemia is available 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.

References
<table>
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<th>Date</th>
<th>Comments</th>
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<td>05/01/16</td>
<td>New Policy; renumbered from 12.04.104. Approved April 12, 2016. All information specific to preconception (carrier) testing moved to 12.04.518 Carrier Testing for Genetic Diseases. Policy is effective 5/1/16.</td>
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<tr>
<td>11/24/16</td>
<td>Policy moved to new format; no change in policy statements.</td>
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<tr>
<td>05/01/17</td>
<td>Annual review, approved April 11, 2017. Policy updated with literature review through December 20, 2016; references 13-14 added. The policy is revised with updated genetics nomenclature; “mutation” changed to “variant”. The intent of the policy statements is unchanged.</td>
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