MEDICAL POLICY – 12.04.519
Genetic Testing for Alpha Thalassemia

BCBSA Ref. Policy: 2.04.104

Effective Date: May 1, 2018
Last Revised: Sept. 1, 2018
Replaces: 12.04.104

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

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 gene variants 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 gene variant 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
<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis of alpha thalassemia</strong></td>
<td>Genetic testing to confirm a diagnosis of alpha thalassemia is considered not medically necessary.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testing</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognosis of alpha thalassemia intermedia</strong></td>
<td>Genetic testing to determine the prognosis of patients with hemoglobin H disease (alpha thalassemia intermedia) is considered investigational.</td>
</tr>
<tr>
<td><strong>Other clinical situations</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>81257</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring) (new code effective 1/1/18)</td>
</tr>
<tr>
<td>81258</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant (new code effective 1/1/18)</td>
</tr>
<tr>
<td>81259</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence (new code effective 1/1/18)</td>
</tr>
<tr>
<td>81269</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants (new code effective 1/1/18)</td>
</tr>
</tbody>
</table>

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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 (see Table 1). 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 2 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>
</tr>
</thead>
<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>
</tr>
</tbody>
</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>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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

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

Alpha-Thalassemia Epidemiology

Alpha-thalassemia is a common genetic disorder, affecting approximately 5% of the world's population.\(^1\) 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. By contrast, for individuals of northern European ancestry, the carrier rate is less than 1 in 1000.

Physiology

Hemoglobin, which is the major oxygen-carrying protein molecule of red blood cells (RBCs), consists of 2 α-globin chains and 2 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\(^2\):

- Ineffective erythropoiesis in the bone marrow.
- Production of nonfunctional hemoglobin molecules.
- Shortened survival of RBCs 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 4 genes that code for α-globin (2 copies each of \(HBA1\) and \(HBA2\), located on chromosome 16), with the wild genotype (normal) being \(\alpha\alpha/\alpha\alpha\). 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. There are 4 different syndromes, which 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 in 1 of 2 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 (HbH) disease (α-thalassemia intermedia):** This syndrome results from three abnormal α-globin genes (a/-/-), resulting in moderate to severe anemia. In HbH 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 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 nondeletion variant typically have an earlier presentation, more severe anemia, jaundice, and bone changes, and more frequently require transfusions.

- **Hemoglobin Bart’s syndrome (α-thalassemia major):** This syndrome results from variants in all 4 α-globin genes (αα/αα), which prevents the 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.

**Genetic Testing**

A number of different types of genetic abnormalities are associated with α-thalassemia. More than 100 genetic variants have been described. Deletion of one or more of the α-globin chains is the most common genetic defect. This type of genetic defect is 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 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). 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.\textsuperscript{5-7} 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 single nucleotide variants.\textsuperscript{4}

**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 a
prognosis of the 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.

**Ongoing and Unpublished Clinical Trials**

A search of [ClinicalTrials.gov](https://clinicaltrials.gov) in December 2017 did not identify any ongoing or unpublished
trials that would likely influence this review.

**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 Amendments (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


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tr>
<tr>
<td>11/24/16</td>
<td>Policy moved to new format; no change in policy statements.</td>
</tr>
<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>
</tr>
<tr>
<td>02/23/18</td>
<td>Coding update, added CPT codes 81258, 81259, and 81269 (new codes effective 1/1/18). Formatting edits were made.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through December 2017; no references added. Policy statements unchanged.</td>
</tr>
<tr>
<td>09/01/18</td>
<td>Coding update, added note to CPT code 81257 (new code effective 1/1/18). Removed CPT code 81404.</td>
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</table>

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
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