Medical Policy
Genetic Testing for Alpha Thalassemia

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Policy Number: 520
BCBSA Reference Number: 2.04.104
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
Preimplantation Genetic Testing, #088

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genetic testing to confirm a diagnosis of alpha thalassemia is considered **NOT MEDICALLY NECESSARY**.

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

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.

*Biochemical testing consists of complete blood count (CBC), microscopic examination of the peripheral blood smear, and hemoglobin electrophoresis.

Genetic testing for alpha thalassemia in other clinical situations (recognizing that prenatal testing is not addressed in this policy) is considered **INVESTIGATIONAL**.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

This is not a covered service.

**Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)**
For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information

Inpatient
• For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
• For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Product/Plan</th>
<th>Prior Authorization Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>Prior authorization is not required.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is not required.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>This is not a covered service.</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<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; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)</td>
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<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</td>
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<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</td>
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<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</td>
</tr>
</tbody>
</table>

HCPCS Codes

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>S3845</td>
<td>Genetic testing for alpha-thalassemia</td>
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</table>
**Description**

**ALPHA-THALASSEMIA**

Alpha-thalassemia is a common genetic disorder, affecting approximately 5% of the world's population. 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 beta-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 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 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 αα/αα. 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 below.

**Silent Carrier**

Silent carrier (α-thalassemia minima) arises from 1 of 4 abnormal α genes (αα/α-) 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**

Thalassemia trait (α-thalassemia minor), also called α-thalassemia trait, arises from the loss of 2 α-globin genes, resulting in 1 of 2 genotypes (αα/-- or α-/α-). Mild anemia is present, and RBCs are hypochromic and microcytic. Clinical symptoms are usually absent and, in most cases, the hemoglobin electrophoresis is normal.

**Hemoglobin H Disease**

Hemoglobin H (HbH) disease (α-thalassemia intermedia) results from 3 abnormal α-globin genes (α-/--), resulting in moderate-to-severe anemia. In HbH disease, there is an imbalance in α- 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 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. They 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**
Hemoglobin Bart’s (α-thalassemia major) results from variants in all 4 α-globin genes (--/--), 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 during pregnancy for a woman carrying a fetus with hydrops fetalis. They include hypertension, preeclampsia, antepartum hemorrhage, renal failure, premature labor, and abruption placenta.¹

**Genetic Testing**
A number of 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.¹ Large genetic rearrangements can also occur from defects in crossover and/or recombination of genetic material during reproduction. Single nucleotide variants in one or more of the α genes 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 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.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.⁴

**Summary**
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 4 α-globin genes are causative of these syndromes. Rates of variants in the α-thalassemia gene vary across ethnic groups and are highest in individuals from Southeast Asia, Africa, and the Mediterranean region.

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.

For individuals who have biochemical evidence of α-thalassemia who are considering conception who receive genetic testing for α-thalassemia, the evidence 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 α-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 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 α-thalassemia trait. Therefore, these tests 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
## Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>4/2018</td>
<td>BCBSA National medical policy review. Policy format updated. Policy statements unchanged. 4/1/2018</td>
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<tr>
<td>1/2018</td>
<td>Clarified coding information.</td>
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<tr>
<td>4/2017</td>
<td>BCBSA National medical policy review. Policy clarified. Policy statements unchanged. 4/1/2017</td>
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<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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<tr>
<td>8/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes. Effective 10/2015.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- [Medical Policy Terms of Use](#)
- [Managed Care Guidelines](#)
- [Indemnity/PPO Guidelines](#)
- [Clinical Exception Process](#)
- [Medical Technology Assessment Guidelines](#)

**References**


