Medical Policy

Genetic Testing for Alpha Thalassemia

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Policy Number: 520
BCBSA Reference Number: 2.04.104

Related Policies

- Preimplantation Genetic Testing, #088

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

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

Preconception (carrier) testing for alpha thalassemia in prospective parents may be considered **MEDICALLY NECESSARY** when both parents have evidence of 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 smear, and Hgb electrophoresis.

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

Prior Authorization Information

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.

Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th>Commercial Managed Care (HMO and POS)</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td></td>
<td>Medicare HMO Blue℠</td>
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<tr>
<td></td>
<td>Medicare PPO Blue℠</td>
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</table>
CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. 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. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

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

### 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, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)</td>
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</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>

### ICD-9 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-9-CM-diagnosis codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>V26.31</td>
<td>Testing of female for genetic disease carrier status</td>
</tr>
<tr>
<td>V26.34</td>
<td>Testing of male for genetic disease carrier status</td>
</tr>
<tr>
<td>282.43</td>
<td>Alpha thalassemia</td>
</tr>
<tr>
<td>282.46</td>
<td>Thalassemia minor</td>
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### ICD-10 Diagnosis Codes

<table>
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<th>ICD-10-CM-diagnosis codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>Z31.430</td>
<td>Encounter Of Female For Testing For Genetic Disease Carrier Status For Procreative Management</td>
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<tr>
<td>Z31.440</td>
<td>Encounter Of Male For Testing For Genetic Disease Carrier Status For Procreative Management</td>
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<tr>
<td>D56.0</td>
<td>Alpha Thalassemia</td>
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<tr>
<td>D56.3</td>
<td>Thalassemia minor</td>
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### Description

Hemoglobin, which is the major oxygen carrying protein molecule of red blood cells, 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:

- 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 aa/aa. Genetic mutations may occur in any or all of these 4 α-globin genes. The number of genetic mutations 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 1 of 4 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 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 Hgb electrophoresis is normal.

- **Hemoglobin H disease (α-thalassemia intermedia).** This syndrome results from 3 abnormal α-globin genes (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. Additional 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.

- **Hemoglobin Bart syndrome (α-thalassemia major).** This syndrome results from mutations 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.

There is an association between genotype and phenotype among patients with HgH disease. Individuals with a nondeletion mutation typically have an earlier presentation, more severe anemia, jaundice, and bone changes, and more frequently require transfusions.

Genetic Testing
A number of different types of genetic abnormalities are associated with α-thalassemia. More than 100 different genetic mutations have been described. Deletion of 1 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. Large genetic rearrangements can also occur from defects in crossover and/or recombination of genetic material during reproduction. Point mutations in 1 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 mutation analysis for known α-globin gene mutations 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 mutations, 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 mutations.

**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 \( \alpha \)-globin genes are causative of these syndromes. The rate of mutations in the \( \alpha \)-thalassemia gene varies across ethnic groups, and is highest in individuals from Southeast Asia, Africa, and the Mediterranean region.

The diagnosis of the \( \alpha \)-thalassemia syndromes that have clinical implications can be made based on biochemical testing without the need for genetic testing. As a result, genetic testing for confirmation of the diagnosis of \( \alpha \)-thalassemia is considered not medically necessary.

For patients with hemoglobin H disease, there may be a genotype-phenotype correlation for disease severity, but there is not currently evidence to indicate that patient management or outcomes would be altered by through genetic testing. Therefore, genetic testing for determining the prognosis of hemoglobin H disease is considered investigational.

Preconception (carrier) testing is intended to avoid the most serious form of \( \alpha \)-thalassemia, hemoglobin Bart disease. 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 mutations is present in \( \alpha \)-thalassemia trait. They therefore cannot completely determine the risk of a pregnancy with hemoglobin Bart syndrome 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, genetic testing may be considered medically necessary for carrier screening in parents who have evidence suggestive of \( \alpha \)-thalassemia trait or disease on the basis of hemoglobin electrophoresis or CBC and peripheral smear.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<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**


