| 2.04.104 | Genetic Testing for Alpha Thalassemia | | |
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| **Section:** | 2.0 Medicine | **Page:** | Page 1 of 15 |

## Policy Statement

I. Genetic testing to confirm a diagnosis of alpha thalassemia is considered **investigational**.

II. Genetic testing of individuals with hemoglobin H disease (alpha thalassemia intermedia) to determine prognosis is considered **investigational**.

III. 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 minima [silent carrier] ) based on biochemical testing (see Policy Guidelines section).

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

**NOTE**: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

Biochemical testing to determine whether α-thalassemia is present should be the first step in evaluating the presence of the condition. Biochemical testing consists of complete blood count (CBC), microscopic examination of the peripheral blood smear, and hemoglobin electrophoresis. In silent carriers and in α-thalassemia trait, the hemoglobin electrophoresis will most likely be normal. However, there should be evidence of possible α-thalassemia minor on the CBC and peripheral smear.

The probability of a pregnancy with hemoglobin Bart's (α-thalassemia major) depends on the specific genotype found in each parent. Table PG1 summarizes the risk according to each category of α-thalassemia.

**Table PG1. Risk of α-Thalassemia**

| Clinical Diagnosis in Parents | Genotype (Parent 1) | Genotype (Parent 2) | Probability of Hemoglobin Bart's, % |
|---|---|---|---|
| **Both parents silent carriers** | αα/α- | αα/α- | 0 |
| **1 parent silent carrier, 1 parent trait** | αα/α- | α-/α- | 0 |
| | | αα/α- | 0 |
| **Both parents trait** | αα/-- | αα/-- | 25 |
| | | α-/α- | 0 |
| | α-/α- | αα/-- | 0 |
| | | α-/α- | 0 |
| **1 parent HbH, 1 parent silent carrier** | α-/-- | αα/α- | 0 |
| **1 parent HbH, 1 parent trait** | α-/-- | αα/-- | 25 |
| | | α-/α- | 0 |
| **Both parents HbH** | α-/-- | α-/-- | 25 |

HbH: hemoglobin H.

This policy does not address prenatal (in utero or preimplantation) genetic testing for α-thalassemia.

### 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 PG2. Nomenclature to Report on Variants Found in DNA**

| Previous | Updated | Definition |
|---|---|---|
| **Mutation** | Disease-associated variant | Disease-associated change in the DNA sequence |
| | Variant | Change in the DNA sequence |
| | Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

**Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification**

| Variant Classification | Definition |
|---|---|
| **Pathogenic** | Disease-causing change in the DNA sequence |
| **Likely pathogenic** | Likely disease-causing change in the DNA sequence |
| **Variant of uncertain significance** | Change in DNA sequence with uncertain effects on disease |
| **Likely benign** | Likely benign change in the DNA sequence |
| **Benign** | Benign change in the DNA sequence |

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

### Genetic Counseling

Genetic counseling is primarily aimed at individuals 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.

## Description

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. Rates of variants in the $\alpha$-thalassemia gene vary across ethnic groups and are highest in individuals from Southeast Asia, Africa, and the Mediterranean region.

## Related Policies

- Genetic Testing: Preimplantation Genetic Testing

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

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

## Rationale

### Background

### Alpha-Thalassemia

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 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 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.[3,]

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.[1,] 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.[4,]

### 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 1 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.[4,] Large genetic rearrangements can also occur from defects in crossover and/or recombination of genetic material during reproduction. Single nucleotide variants in 1 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, including chromosomal microarray analysis using oligonucleotide or SNP arrays, and next-generation sequencing (NGS) for analysis of deletion breakpoints.

## Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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.[5,6,7,8,9,10,11,]

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

### Testing for Patients With Suspected α-Thalassemia

#### Clinical Context and Test Purpose

The purpose of genetic testing of individuals who are suspected to have α-thalassemia based on clinical signs and symptoms is to confirm a diagnosis and inform clinical decisions such as initiating treatment with iron supplementation, folic acid, or blood transfusion that improve the net health outcome.

The following PICO was used to select literature to inform this review.

##### *Populations*

The relevant population of interest is individuals who are suspected to have α-thalassemia based on clinical signs and symptoms.

##### *Interventions*

The test being considered is genetic testing for the diagnosis of α-thalassemia.

##### *Comparators*

Biochemical testing, including complete blood count and hemoglobin electrophoresis, is currently being used to make diagnostic decisions about individuals who are suspected to have α-thalassemia.

##### *Outcomes*

The general outcomes of interest are related to the requirement and frequency of interventions for the management of anemia such as iron supplementation, folic acid supplementation, chelation therapy, and blood transfusion.

The potentially beneficial outcomes of primary interest would be improvements in overall or disease-specific survival and reduction in morbid events as a result of the timely initiation of appropriate treatment.

The potentially harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to the unnecessary initiation of treatment. False-negative test results can lead to lack of initiation of appropriate treatment.

The primary outcomes of interest are related to the short-term improvement in signs and symptoms of α-thalassemia and long-term survival after initiation of treatment.

### Study Selection Criteria

For the evaluation of clinical validity of genetic testing for α-thalassemia, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

### Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

### Review of Evidence

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

Henderson et al (2016) reported on a retrospective study assessing genotype and phenotype correlations of the novel thalassemia and abnormal hemoglobin variants identified after the 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.[12,] Of a total of approximately 12,000 samples, 15 novel $\alpha^+$thalassemia variants, 19 novel β variants, and 11 novel β-globin variants were detected. A 2019 Chinese study of over 15,000 samples that utilized both next-generation sequencing and PCR reported similar numbers of α-thalassemia (n=19) and β -thalassemia (n=21) variants.[13,]

### Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

### Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

The diagnosis of α-thalassemia can be made without genetic testing. This is first done by analyzing 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 indices who are not found to have an 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 hemoglobin H (HbH) disease (α-thalassemia intermedia) by identifying the types and amounts of abnormal hemoglobin present. In the carrier states, greater than 95% of the hemoglobin molecules are normal (hemoglobin A), with a small minority of hemoglobin $A_2$ present (1%-3%).[3,] Alpha-thalassemia intermedia is diagnosed by finding a substantial portion of hemoglobin H (1%-30%) on

electrophoresis. In α-thalassemia major, the majority of the hemoglobin is abnormal, in the form of hemoglobin Bart's (85%-90%).

However, biochemical testing, including CBC and hemoglobin electrophoresis, cannot always reliably distinguish between the asymptomatic carrier state and α-thalassemia trait, because 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 overlap in red blood cell 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 red blood cell 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.

**Section Summary: Testing for Patients With Suspected α-Thalassemia**
The clinical validity of genetic testing for α-thalassemia is high, especially when the causative variant is a large deletion of 1 or more α-globin genes. When a single nucleotide variant is present, the clinical validity may be less certain. The clinical usefulness of genetic testing for α-thalassemia for confirming a diagnosis in individuals who are suspected to have α-thalassemia is low. Confirmation of a diagnosis of α-thalassemia that is clinically actionable can generally be made by nongenetic testing, and therefore there is little utility to genetic testing.

**Testing for Patients With Hemoglobin H Disease**
**Clinical Context and Test Purpose**
The purpose of genetic testing of individuals who have been diagnosed with HbH disease (α-thalassemia intermedia) based on clinical signs and symptoms is to confirm a diagnosis and inform clinical decisions such as initiating treatment with iron supplementation, folic acid, or blood transfusion that improve the net health outcome.

The following PICO was used to select literature to inform this review.

*Populations*
The relevant population of interest is individuals who have been diagnosed with HbH disease based on clinical signs and symptoms.

*Interventions*
The test being considered is genetic testing for α-thalassemia.

*Comparators*
Biochemical testing, including complete blood count and hemoglobin electrophoresis, is currently being used to aid in prognosis and management of individuals who have been diagnosed with HbH disease.

*Outcomes*
The general outcomes of interest are related to the requirement and frequency of interventions for the management of anemia such as iron supplementation, folic acid supplementation, chelation therapy, and blood transfusion.

The potentially beneficial outcomes of primary interest would be improvements in overall or disease-specific survival and reduction in morbid events as a result of the timely initiation of appropriate treatment.

The primary outcomes of interest are related to the short-term improvement in signs and symptoms of α-thalassemia and long-term survival after initiation of treatment.

### Study Selection Criteria

For the evaluation of clinical validity of genetic testing for α-thalassemia, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

### Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

### Review of Evidence

See the discussion on clinical validity in the section titled Testing for Patients With Suspected α-Thalassemia.

### Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

### Direct Evidence

Among patients with HbH disease, there is heterogeneity in the nature of the variant (i.e., deletional vs. nondeletional), with differences across geographic areas and ethnic groups.[14,] Patients with deletional variants may have a less severe course of illness than those with nondeletional variants.[15,] In a 2009 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.[16,] The evidence suggests that different genetic variants leading to α-thalassemia are associated with different prognoses. New treatments for some complications of HbH disease that result from ineffective erythropoiesis and iron overload and may differ for genotypes are under development. However, no evidence was identified to indicate that patient management or outcomes would be changed by prognostic testing.

### Section Summary: Testing for Patients With Hemoglobin H Disease

The clinical usefulness of genetic testing for α-thalassemia for prognostic testing of individuals who have been diagnosed with HbH disease based on clinical signs and symptoms is low. For patients with HbH disease, genetic testing can differentiate between α-thalassemia minima and α-thalassemia minor. However, this distinction is not clinically important because both states are asymptomatic conditions that do not require specific medical care treatment. There may be a genotype-phenotype correlation for disease severity; however, no studies were identified that suggested patient management or outcomes would be altered by genetic testing; therefore, genetic testing for determining the prognosis of HbH disease is not associated with improved clinical utility.

## Testing for Patients Diagnosed With α-Thalassemia Who are Considering Conception

### Clinical Context and Test Purpose

The purpose of genetic testing of individuals diagnosed with α-thalassemia based on clinical signs and symptoms who are considering conception is to define the likelihood of α-thalassemia major in a prospective pregnancy.

The following PICO was used to select literature to inform this review.

*Populations*
The relevant population of interest is individuals who have been diagnosed with α-thalassemia based on clinical signs and symptoms who are considering conception.

*Interventions*
The test being considered is genetic testing for determination of the number or pattern of abnormal alpha genes.

*Comparators*
Biochemical testing, including CBC and hemoglobin electrophoresis, is being used to make diagnostic decisions about individuals with α-thalassemia.

*Outcomes*
The potential major beneficial outcome is avoiding a pregnancy with α-thalassemia major, which is of benefit to a prospective mother or a couple who can make reproductive decisions about the possibility of a nonviable pregnancy, and avoid increased obstetrical complications associated with a fetus with α-thalassemia major.

The potentially harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary termination of an otherwise normal pregnancy. False-negative test results can lead to a full-term carriage of an otherwise nonviable pregnancy and the increased obstetrical complications associated with a fetus with α-thalassemia major.

The timing of avoidance of a nonviable pregnancy would be anytime during the reproductive age of the individuals with α-thalassemia.

### Study Selection Criteria
For the evaluation of clinical validity of genetic testing for α-thalassemia, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

### Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

### Review of Evidence
See the discussion on clinical validity in the section titled Testing for Patients With Suspected α-Thalassemia.

### Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

### Direct Evidence
Carrier screening with biochemical testing is recommended for all patients who are from ethnic groups with a high incidence of α-thalassemia. Biochemical screening consists of a CBC with peripheral smear analysis. If their abnormalities are noted (e.g., anemia, microcytosis, hypochromia),

hemoglobin electrophoresis is then performed to identify the specific types of hemoglobin present. As noted, the hemoglobin electrophoresis may be normal in the asymptomatic carrier and α-thalassemia trait states, but the states may be suspected based on CBC and peripheral smear analysis.

Unlike clinical diagnosis, for carrier testing, it is important to distinguish between α-thalassemia carrier (1 abnormal gene) and α-thalassemia trait (2 abnormal genes), and important to distinguish between the 2 variants of α-thalassemia trait, i.e., the αα/-- (*cis* variant) and the α-/α- (*trans* variant). This is important because only when both parents have the αα/-- *cis* variant is there a risk for a fetus with α-thalassemia major.[17,] When both parents are α-thalassemia carriers (αα/--), there is a 1 in 4 likelihood that an offspring will have α-thalassemia major and hydrops fetalis. These parents may decide to pursue preimplantation genetic diagnosis in conjunction with in vitro fertilization to avoid a pregnancy with hydrops fetalis.

In this situation, genetic testing has incremental utility over biochemical testing. Whereas biochemical testing can determine whether a silent carrier/trait syndrome is present, and can distinguish those syndromes from HbH disease, it cannot provide a precise determination of the number or pattern of abnormal alpha genes. As a result, using biochemical screening alone, the probability of developing a hemoglobin Bart's fetus cannot be accurately assessed. By contrast, genetic testing can delineate the number of abnormal genes with certainty. Also, genetic testing can determine whether an α-thalassemia trait exists as the *cis* (αα/--) variant or the *trans* (α-/α-) variant. Using this information from genetic testing, the probability of hemoglobin Bart's can be determined according to Table 1.

**Table 1. Probability of Hemoglobin Bart's**

| Clinical Diagnosis in Parents | Genotype (Parent 1) | Genotype (Parent 2) | Probability of Hemoglobin Bart's, % |
|---|---|---|---|
| **Both parents silent carriers** | αα/α- | αα/α- | 0 |
| **1 parent silent carrier, 1 parent trait** | αα/α- | α-/α- | 0 |
| | | αα/α- | 0 |
| **Both parents trait** | αα/-- | αα/-- | 25 |
| | | α-/α- | 0 |
| | α-/α- | αα/-- | 0 |
| | | α-/α- | 0 |
| **1 parent HbH, 1 parent silent carrier** | α-/-- | αα/α- | 0 |
| **1 parent HbH, 1 parent trait** | α-/-- | αα/-- | 25 |
| | | α-/α- | 0 |
| **Both parents HbH** | α-/-- | α-/-- | 25 |

HbH: hemoglobin H.

Parents can also determine the likelihood of HbH disease in an offspring through genetic testing. However, because this is a mild condition in most cases, it is less likely to be considered information that is actionable in terms of altering reproductive decision making.[17,]

### Section Summary: Testing for Patients Diagnosed With α-Thalassemia Who are Considering Conception

Preconception (carrier) testing is likely to have clinical usefulness by providing incremental diagnostic information over biochemical testing. Genetic testing can identify the pattern of abnormal α genes and estimate more precisely the risk of hydrops fetalis.

### Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### American College of Obstetricians and Gynecologists

In 2017, the American College of Obstetricians and Gynecologists published an opinion document that includes multiple general recommendations about carrier screening of genetic conditions.[18,] Specific descriptions of genetic testing for α-thalassemia include the following: DNA-based genetic testing should be used to detect α-*globin* gene characteristics of suspected cases of thalassemia "[i]f the mean corpuscular volume is below normal, iron deficiency anemia has been excluded, and the hemoglobin [Hb] electrophoresis is not consistent with β-thalassemia trait (i.e., there is no elevation of Hb $A_2$ or Hb F)."

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

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

### Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in April 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

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## Documentation for Clinical Review

**Please provide the following documentation:**

- History and physical and/or consultation notes including:
  - Family history
  - How test result will impact clinical decision making
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
- Lab results documenting both partners carrier status or genetic disorder
- Provider order for genetic test
- Name and description of genetic test
- CPT codes billed for the particular genetic test

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

| Type | Code | Description |
|---|---|---|
| CPT® | 81257 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring) |
| | 81258 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant |
| | 81259 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence |
| | 81269 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants |
| HCPCS | Non | |

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action |
|---|---|
| 10/31/2014 | BCBSA medical policy adoption |
| 01/01/2017 | Policy revision without position change |
| 04/01/2017 | Policy revision without position change |
| 02/01/2018 | Coding update |
| 04/01/2018 | Policy revision without position change |
| 09/01/2019 | Policy revision without position change |
| 08/01/2023 | Policy reactivated. Previously archived from 04/01/2020 to 07/31/2023. |

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and

effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

## Appendix A

| POLICY STATEMENT | |
|---|---|
| **BEFORE** | **AFTER**<br>Blue font: Verbiage Changes/Additions |
| **Reactivated Policy**<br><br>**Policy Statement:**<br>N/A | **Genetic Testing for Alpha Thalassemia 2.04.104**<br><br>**Policy Statement:**<br>I. Genetic testing to confirm a diagnosis of alpha thalassemia is considered **investigational**.<br><br>II. Genetic testing of individuals with hemoglobin H disease (alpha thalassemia intermedia) to determine prognosis is considered **investigational**.<br><br>III. 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 minima [silent carrier] ) based on biochemical testing (see Policy Guidelines section).<br><br>IV. Genetic testing for alpha thalassemia in other clinical situations (recognizing that prenatal testing is not addressed in this policy) is considered **investigational**. |