Diagnostic Genetic Testing for α-Thalassemia

Effective: May 1, 2025

Next Review: January 2026
Last Review: March 2025

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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 four α-globin genes are causative of these syndromes.

MEDICAL POLICY CRITERIA

Note: This policy applies to diagnostic testing only. Reproductive carrier screening is addressed separately (see Cross References).

I. Diagnostic prenatal (fetal) genetic testing for α-thalassemia may be considered **medically necessary**.

II. Diagnostic genetic testing to confirm a diagnosis of α-thalassemia is considered **not medically necessary**.

III. Diagnostic genetic testing for α-thalassemia in other clinical situations is considered **investigational**, including in patients with hemoglobin H disease (alpha-thalassemia intermedia) to determine prognosis.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Strategies for testing may include testing for individual genes or in combination, such as in a panel.

Alpha-thalassemias include:

- Thalassemia trait (α-thalassemia minor)
- Hemoglobin H Disease (α-thalassemia intermedia)
- Hemoglobin Bart's (α-thalassemia major, hydrops fetalis)

BIOCHEMICAL TESTING

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.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION:

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
    - History and physical exam including any relevant diagnoses related to the genetic testing
    - Conventional testing and outcomes
    - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
3. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

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 two α-globin chains and two 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 four genes that code for α-globin (two 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 four α-globin genes. The number of genetic variants determines the phenotype and severity of the α-thalassemia syndromes. There are four different syndromes, which are classified below.

Silent Carrier

Silent carrier (α-thalassemia minima) arises from one of four 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 two α-globin genes, resulting in one of two 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 three 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.[2]

HbH has marked phenotypic variability, but most individuals have mild disease.[3] Splenomegaly is common and can lead to the need for splenectomy, for which transfusion support may be required.[1] Iron chelation therapy may be indicated for increased iron deposition. Inappropriate iron therapy and oxidant drugs that can exacerbate hemolysis should

be avoided in patients with HbH disease. A minority of people with HbH develop jaundice, hepatomegaly, and mild to moderate skeletal changes associated with thalassemia (e.g., hypertrophy of the maxilla, bossing of the skull).[3]

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 four α-globin genes (--/--), which prevents 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 different types of genetic abnormalities on the *HBA1* and *HBA2* genes are associated with α-thalassemia. 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.[3] Large genetic rearrangements can also occur from defects in crossover and/or recombination of genetic material during reproduction. Point mutations 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 using Gap polymerase chain reaction (Gap-PCR) or sequence analysis. Newer testing methods used to detect α-thalassemia variants include multiplex amplification methods and next generation sequencing (NGS).[3]

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 regulatory standards of the Clinical Laboratory 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 this test.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[4] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

GENETIC TESTING FOR ALPHA-THALASSEMIA

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

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.[5-11]

Analytic Validity

A variety of testing methods can be used to evaluate the two 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.[12] Reproducibility of the assay was high. In the clinical samples, there was 100% concordance between the 20 genotypes identified and the genotyping method. Petropoulou (2015) evaluated a PCR-based high-resolution melting curve analysis of duplicated areas of the *HBA1 and HBA2* genes with novel nondeletion variants.[13] 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 one 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.

Henderson (2016) 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.[14] Of a total of approximately 12,000 samples, 15 novel α-thalassemia variants, 19 novel β-thalassemia 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. Prenatal (in utero) testing can also be performed to determine the presence and type of α-thalassemia of a fetus. Prenatal testing is not addressed in this evidence review.

Confirming a Diagnosis

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 (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 hemoglobin molecules are normal (hemoglobin A), with a small minority of hemoglobin A_2 present (1%-3%).[15] Alpha-thalassemia intermedia is diagnosed by finding a substantial portion of hemoglobin H (1%-30%) on electrophoresis.[15] In α-thalassemia major, the majority of the hemoglobin is abnormal, in the form of hemoglobin Bart's (85%-90%).[15]

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 measuring 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 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 HbH disease, there is heterogeneity in the nature of the variant (i.e., deletional vs. nondeletional), with differences across geographic areas and ethnic groups.[16] Patients with deletional variants may have a less severe course of illness than those with nondeletional variants.[16] 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.[17]

The evidence suggests that different genetic variants leading to α-thalassemia are associated with different prognoses.[18] However, clinical diagnosis can be made based on red cell indices to guide therapy, and no evidence was identified to indicate that patient management or outcomes would be changed by prognostic testing.[19]

Section Summary: Clinical Utility

The clinical utility of genetic testing for α-thalassemia may occur in several settings. For confirming a diagnosis of α-thalassemia, because the diagnosis of clinically actionable types can generally be made on the basis of nongenetic testing, there is little utility to genetic testing. For patients with HbH disease, 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.

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.

SUMMARY

There is enough research to show that prenatal testing for α-thalassemia can improve health outcomes. Prenatal fetal testing informs reproductive decision making, including decisions regarding continuation of the pregnancy, birthing decisions, and enabling for timely treatment of a condition that could be treated either in utero or immediately after birth. Therefore, prenatal testing for α-thalassemia may be considered medically necessary.

There is enough research to show that diagnosis of α-thalassemia syndromes can be made based on biochemical testing without genetic testing. Therefore, genetic testing to confirm a diagnosis of α-thalassemia is considered not medically necessary.

There is not enough research to show that genetic testing for α-thalassemia can improve health outcomes for patients with any other conditions, including people who have hemoglobin H disease (α-thalassemia intermedia). In addition, there are no clinical guidelines based on research that recommend this testing. Therefore, genetic testing is considered investigational for patients with hemoglobin H disease or for other clinical situations.

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CODES

Codes	Number	Description
CPT	81257	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)
	81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
	81259	;full gene sequence
	81269	;duplication/deletion variants
	81404	Molecular pathology procedure level 5
HCPCS	None	

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