
Medical Policy



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***Current Policy Effective Date: 3/1/21**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Alpha-Thalassemia

Description/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 ($\alpha\alpha/\alpha-$), 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 ($\alpha\alpha/--$, or $\alpha-/ \alpha-$). 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 ($\alpha/--$), 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 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 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. Point mutations 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, 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 point variants.(4)

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.

Medical Policy Statement

The safety and effectiveness of genetic testing for α -thalassemia for specified populations has been established. It may be considered a useful therapeutic option for patients who meet specific selection criteria.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Preconception (carrier) testing for α -thalassemia in prospective parents may be considered established when the following are met:

- Based on biochemical testing, one or both parents have evidence of:
 - α -thalassemia (including α -thalassemia minor **or** hemoglobin H disease (α -thalassemia intermedia) **OR**
 - α -thalassemia major

Exclusions:

- Genetic testing to confirm a diagnosis of α -thalassemia
- Genetic testing of patients with hemoglobin H disease (alpha-thalassemia intermedia) to determine prognosis
- Genetic testing in other clinical situations

*See Policy Guidelines for more information

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81257 81258 81259 81269

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

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) is dependent 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	$\alpha\alpha/\alpha-$	$\alpha\alpha/\alpha-$	0
One parent silent carrier, 1 parent trait	$\alpha\alpha/\alpha-$	$\alpha-/ \alpha-$	0
		$\alpha\alpha/\alpha-$	0
Both parents trait	$\alpha\alpha/--$	$\alpha\alpha/--$	25
		$\alpha-/ \alpha-$	0
	$\alpha-/ \alpha-$	$\alpha\alpha/--$	0
		$\alpha-/ \alpha-$	0
One parent HbH, 1 parent silent carrier	$\alpha-/ --$	$\alpha\alpha/\alpha-$	0
One parent HbH, 1 parent trait	$\alpha-/ --$	$\alpha\alpha/--$	25
		$\alpha-/ \alpha-$	0
Both parents HbH	$\alpha-/ --$	$\alpha-/ --$	25

HbH: hemoglobin H.

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

Genetic Testing for Alpha Thalassemia

Evidence indicates that confirmation of diagnosis in individuals who have suspected alpha-thalassemia can be verified based on biochemical testing without the need for genetic testing.

There is some evidence for a genotype-phenotype correlation with disease severity in individuals with hemoglobin H disease (alpha-thalassemia intermedia). However, there is no current evidence to indicate that patient management or outcomes would be altered. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.

Preconception (carrier) testing is intended to avoid the most serious form of alpha-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 (CBC), along with peripheral smear. For individuals who are considering conception and have biochemical confirmation of alpha-thalassemia, the evidence is sufficient to determine that genetic testing for alpha-thalassemia results in a meaningful improvement in the net health outcome.

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 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.

Rationale

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.(5,6,8-12)

TESTING FOR PATIENTS WITH SUSPECTED ALPHA-THALASSEMIA OR WITH HEMOGLOBIN H DISEASE

Clinical Context and Test Purpose

The purpose of genetic testing for α -thalassemia is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as standard diagnostic workup for α -thalassemia, in patients with suspected α -thalassemia based on clinical signs and symptoms. Additionally, genetic testing can be used 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 question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals who are suspected to have α -thalassemia or those who have been diagnosed with HbH disease?

The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest are individuals who are suspected to have α -thalassemia or those who have been diagnosed with HbH disease based on clinical signs and symptoms. Individuals with thalassemia may be treated either in an outpatient setting by family practitioners or in specialized thalassemia clinics by a multidisciplinary team of physicians.

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 make diagnostic decisions about individuals who are suspected to have α -thalassemia or 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 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.

Simplifying Test Terms

There are three core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or predicting a response to therapy.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and

unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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 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 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.(13) Of a total of approximately 12,000 samples, 15 novel α -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.(14)

Section Summary: Clinically Valid

The clinical validity of genetic testing for α -thalassemia is high, especially when the causative variant is a large deletion of one or more α -globin gene. When a single nucleotide variant is present, the clinical validity may be less certain.

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.

Review of Evidence

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.

There are several potential areas for clinical usefulness. 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. Preconception (carrier) testing can be performed to determine the likelihood of an offspring with an α -thalassemia syndrome. 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 (hemoglobin H [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 A₂ present (1%-3%).(3) Alpha-thalassemia intermedia is diagnosed by finding a substantial portion of hemoglobin H (1%-30%) on electrophoresis.(3) In α -thalassemia major, the majority of the hemoglobin is abnormal, in the form of hemoglobin Bart's (85%-90%).(3)

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 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 Hemoglobin H Disease

Among patients with HbH disease, there is heterogeneity in the nature of the variant (ie, deletional vs nondeletional), with differences across geographic areas and ethnic groups. (15) 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.(16) However, no evidence was identified to indicate that patient management or outcomes would be changed by prognostic testing.

Section Summary: Clinically Useful

The clinical usefulness of genetic testing for α -thalassemia either for confirming a diagnosis in individuals who are suspected to have α -thalassemia based on clinical signs and symptoms 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. 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 ALPHA-THALASSEMIA WHO ARE CONSIDERING CONCEPTION

Clinical Context and Test Purpose

The purpose of genetic testing for those who have been 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 question addressed in this evidence review is: Does genetic testing avoid a prospective α -thalassemia major pregnancy in individuals diagnosed with α -thalassemia based on clinical signs and symptoms who are considering conception?

The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest are individuals who have been diagnosed with α -thalassemia based on clinical signs and symptoms who are considering conception. Patients may be referred from primary care to a medical geneticist or counselor for reproductive decision making.

Interventions

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

Comparators

Biochemical testing, including complete blood count 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 a false-positive or false-negative test results. False-positive test results can lead to the 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 major.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist.

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). See the preceding discussion of clinical validity.

See the discussion in the previous section on Clinically Valid.

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.

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 there abnormalities are noted, such as anemia, microcytosis, or 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 (one abnormal gene) and α -thalassemia trait (two abnormal genes), and important to distinguish between the two variants of α -thalassemia trait, ie, the $\alpha\alpha/--$ (cis variant) and the $\alpha-/ \alpha-$ (trans variant). This is important because only when both parents have the $\alpha\alpha/--$ cis variant is there a risk for a fetus with α -thalassemia major.(17) When both parents are α -thalassemia carriers ($\alpha\alpha/--$), there is a one in four 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. In addition, genetic testing can determine whether an α -thalassemia trait exists as the cis ($\alpha\alpha/--$) variant or the trans ($\alpha-/ \alpha-$) 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	$\alpha\alpha/\alpha-$	$\alpha\alpha/\alpha-$	0
One parent silent carrier, 1 parent trait	$\alpha\alpha/\alpha-$	$\alpha-/ \alpha-$	0
		$\alpha\alpha/\alpha-$	0
Both parents trait	$\alpha\alpha/--$	$\alpha\alpha/--$	25
		$\alpha-/ \alpha-$	0
	$\alpha-/ \alpha-$	$\alpha\alpha/--$	0
		$\alpha-/ \alpha-$	0
One parent HbH, 1 parent silent carrier	$\alpha/--$	$\alpha\alpha/\alpha-$	0
One parent HbH, 1 parent trait	$\alpha/--$	$\alpha\alpha/--$	25
		$\alpha-/ \alpha-$	0
Both parents HbH	$\alpha/--$	$\alpha/--$	25

HbH: hemoglobin H.

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

Section Summary: Clinically Useful

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.

Section Summary: Testing for Patients Diagnosed with α -thalassemia Who Are Considering Conception

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.

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.

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. They therefore 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.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

Society of Obstetricians and Gynaecologists of Canada

The Society of Obstetricians and Gynaecologists of Canada (2008) published guidelines on carrier testing for thalassemia.(17) These guidelines included the following recommendations:

1. Carrier screening for α -thalassemia should be offered to all woman from ethnic groups with an increased prevalence of α -thalassemia. Initial screening should consist of "complete blood count, hemoglobin electrophoresis or hemoglobin high performance liquid chromatography...." ferritin testing [and examination of peripheral] blood smear to identify H bodies."
2. If a woman's screening is abnormal ..., then screening the partner should be performed [using the same battery of tests]."
3. "If both partners are found to be carriers of thalassemia ... or of a combination of thalassemia and a hemoglobin variant, they should be referred for genetic counseling.... Additional molecular studies may be required to clarify the carrier status of the parents and thus the risk to the fetus."

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2017) 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 (ie, there is no elevation of Hb A2 or Hb F)."

Government Regulations

National:

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

Local:

There is no local coverage determination (LCD).

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing – Carrier Screening
 - Genetic Testing and Counseling
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/29/20, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/18	4/17/18	4/17/18	Joint policy established
7/1/19	4/16/19		Routine maintenance
3/1/20	12/17/19		Routine maintenance
3/1/21	12/15/20		Routine maintenance

Next Review Date: 4th Qtr, 2021

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR A-THALASSEMIA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- *Duplicate (back-up) equipment is not a covered benefit.*