FEP Medical Policy Manual

FEP 2.04.104 Genetic Testing for α-Thalassemia

Effective Policy Date: October 1, 2023

Original Policy Date: September 2019

Related Policies:

None

Genetic Testing for α-Thalassemia

Description

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

OBJECTIVE

The objective of this evidence review is to determine whether testing for variants in the *HBA1* and *HBA2* genes improves the net health outcome in individuals with suspected or confirmed α-thalassemia.

POLICY STATEMENT

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

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

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

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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

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 insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have hemoglobin H disease (α-thalassemia intermedia) who receive genetic testing for α-thalassemia, the evidence includes case series that correlate specific variants with a prognosis of the disease. Relevant outcomes are overall survival, disease-specific survival, symptoms, and quality of life. There is some evidence for a genotype-phenotype correlation with disease severity, but no current evidence indicates that patient management or outcomes would be altered by genetic testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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 (ie, 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2019	New policy	New policy with literature review through January 3, 2019; Genetic testing to confirm a diagnosis of -thalassemia is considered not medically necessary; genetic testing of patients with hemoglobin H disease (thalassemia intermedia) to determine prognosis is considered investigational; genetic testing for -thalassemia in other clinical situations (recognizing that preconception/prenatal testing is not addressed in this policy) is considered investigational.
September 2020	Replace policy	Policy updated with literature review through May 16, 2020; references added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through May 4, 2021; no references added. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through April 25, 2022; no references added. Policy statements unchanged.
September 2023	Replace policy	Policy updated with literature review through April 25, 2023; reference added. Minor editorial refinements to policy statements; intent unchanged.