Genetic Testing for α-Thalassemia

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

POLICY STATEMENT

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

Genetic testing of patients 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.
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.

**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 PG1). 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 PG2 shows the recommended standard terminology “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” to describe variants identified that cause Mendelian disorders.

<table>
<thead>
<tr>
<th>Table PG1 Nomenclature to Report on Variants Found in DNA</th>
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<tbody>
<tr>
<td><strong>Previous</strong></td>
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<tr>
<td>Mutation</td>
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<tr>
<td>Variant</td>
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<td>Familial variant</td>
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<table>
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<tr>
<th>Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification</th>
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<tr>
<td><strong>Variant Classification</strong></td>
</tr>
<tr>
<td>Pathogenic</td>
</tr>
<tr>
<td>Likely pathogenic</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
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<tr>
<td>Likely benign</td>
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<tr>
<td>Benign</td>
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ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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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.

BENEFIT APPLICATION

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.

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

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. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, symptoms, and QOL. 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 HbH disease who receive genetic testing for α-thalassemia, the evidence includes case series that correlate specific variants with a prognosis of the disease. The relevant outcomes are OS, disease-specific survival, symptoms, and QOL. 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

No published guidelines on testing for thalassemia (non-prenatal/preconception guidelines)

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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.

REFERENCES


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# POLICY HISTORY

This policy was approved by the FEP® Pharmacy and Medical Policy Committee according to the history below:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>September 2019</td>
<td>New policy</td>
<td>New policy with literature review through January 3, 2019; Genetic testing to confirm a diagnosis of α-thalassemia is considered not medically necessary; genetic testing of patients with hemoglobin H disease (α-thalassemia intermedia) to determine prognosis is considered investigational; genetic testing for α-thalassemia in other clinical situations (recognizing that preconception/prenatal testing is not addressed in this policy) is considered investigational.</td>
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