

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA THALASSEMIA
POLICY NUMBER	MP 2.320

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

[POLICY
RATIONALE
CODING INFORMATION](#)

[PRODUCT VARIATIONS
DEFINITIONS
REFERENCES](#)

[DESCRIPTION/BACKGROUND
DISCLAIMER
POLICY HISTORY](#)

I. POLICY

Genetic testing to confirm a diagnosis of α -thalassemia is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Genetic testing of individuals with hemoglobin H disease (α -thalassemia intermedia) to determine prognosis is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Preconception (carrier) testing for α -thalassemia in prospective parents may be considered **medically necessary** when both parents have evidence of possible α -thalassemia (including α -thalassemia minor, hemoglobin H disease [α -thalassemia intermedia], or α -thalassemia minima [silent carrier]) based on biochemical testing (see Policy Guidelines section).

Genetic testing for α -thalassemia in other clinical situations (recognizing that prenatal testing is not addressed in this policy) is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

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

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

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA THALASSEMIA
POLICY NUMBER	MP 2.320

The probability of a pregnancy with hemoglobin Bart's syndrome (alpha 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 parent's 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 parent's 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

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 policy 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

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA THALASSEMIA
POLICY NUMBER	MP 2.320

	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives
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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.

Cross-References:

MP 2.278 Invasive Prenatal (Fetal) Diagnostic Testing
MP 2.326 General Approach to Genetic Testing
MP 7.009 Preimplantation Genetic Testing

II. PRODUCT VARIATIONS

[TOP](#)

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA THALASSEMIA
POLICY NUMBER	MP 2.320

III. DESCRIPTION/BACKGROUND

[TOP](#)

ALPHA-THALASSEMIA

Alpha-thalassemia is a common genetic disorder, affecting approximately 5% of the world's population. 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:

- 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 $\alpha\alpha/\alpha\alpha$. 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 ($\alpha\alpha/\alpha-$) 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 2 α -globin genes, resulting in 1 of 2 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 3 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.

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA THALASSEMIA
POLICY NUMBER	MP 2.320

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. 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.

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.

Genetic Testing

A number of types of genetic abnormalities are associated with α -thalassemia. More than 100 genetic variants have been described. 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. Large genetic rearrangements can also occur from defects in crossover and/or recombination of genetic material during reproduction. Single nucleotide variants 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 by polymerase chain reaction (PCR). 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. 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 single nucleotide variants.

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.

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA THALASSEMIA
POLICY NUMBER	MP 2.320

IV. RATIONALE

[TOP](#)

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 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. Therefore, these tests 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.

V. DEFINITIONS

[TOP](#)

N/A

VI. DISCLAIMER

[TOP](#)

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA THALASSEMIA
POLICY NUMBER	MP 2.320

medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

[TOP](#)

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary; preconception (carrier) testing for alpha thalassemia in prospective parents:

Procedure Codes							
S3845	81257	81258	81259	81269			

ICD-10-CM Diagnosis Codes	Description
D56.0	Alpha thalassemia
D56.3	Thalassemia minor
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management

VIII. REFERENCES

[TOP](#)

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MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA THALASSEMIA
POLICY NUMBER	MP 2.320

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IX. POLICY HISTORY

[TOP](#)

MP 2.320	05/21/2020 Consensus Review. No change to policy statement. References
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MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALPHA THALASSEMIA
POLICY NUMBER	MP 2.320

	updated. FEP variation updated
	04/14/2021 Consensus Review. No change to policy statement. References and coding reviewed.
	07/14/2022 Minor Review. Modified MN statement. Updated FEP and references. Updated coding table by removing CPT 81361-81364 for beta thalassemia. Removed unspecified diagnosis code.
	12/18/2023 Consensus Review. Updated references. No changes to coding.
	12/11/2024 Minor Review. Editorial refinements to MN criteria to state that testing is for Preconception (carrier) testing. NMN statement changed to INV. Updated references. No changes to coding.
	7/29/2025 Consensus Review. No change to policy statement
	09/23/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/09/2026 Retirement Review. EviCore Delegation.

[Top](#)

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