I. Policy

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

Preconception (carrier) testing for alpha thalassemia in prospective parents may be considered **medically necessary** when both parents have evidence of alpha thalassemia based on biochemical testing (see Policy Guidelines).

Genetic testing for alpha 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 conclusion concerning the health outcomes or benefits associated with this procedure.

### Policy Guidelines

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 Hgb electrophoresis.

The probability of a pregnancy with Hgb Bart syndrome (alpha thalassemia major) is dependent on the specific genotype found in each parent. Below is a summary of the risk according to each category of alpha thalassemia:

<table>
<thead>
<tr>
<th>Clinical diagnosis in parents</th>
<th>Genotype (parent 1)</th>
<th>Genotype (parent 2)</th>
<th>Probability of Hgb Bart syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both parents silent carriers</td>
<td>aa/a-</td>
<td>aa/a-</td>
<td>0%</td>
</tr>
<tr>
<td>One parent silent carrier, one parent trait</td>
<td>aa/a-</td>
<td>a/-/a-</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aa/a--</td>
<td>0%</td>
</tr>
<tr>
<td>Both parents trait</td>
<td>aa/-</td>
<td>aa/-</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a/-/a-</td>
<td>0%</td>
</tr>
</tbody>
</table>
**MEDICAL POLICY**

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>GENETIC TESTING FOR ALPHA THALASSEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLICY NUMBER</td>
<td>MP-2.320</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>a-/a-</th>
<th>aa/--</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>One parent HgH, one parent silent carrier</td>
<td>a/-</td>
<td>aa/a-</td>
<td>0%</td>
</tr>
<tr>
<td>One parent HgbH, one parent trait</td>
<td>a/-</td>
<td>aa/--</td>
<td>aa/a-</td>
</tr>
<tr>
<td>Both parents HgH</td>
<td>a/-</td>
<td>a/-</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Cross-reference:*
MP-7.009 Preimplantation Genetic Testing

**II. PRODUCT VARIATIONS**

[N] = No product variation, policy applies as stated  
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids  
[N] PPO  
[N] HMO  
[Y] SeniorBlue HMO**  
[Y] SeniorBlue PPO**

*The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.*

** Refer to Novitas Solutions Local Coverage Determination (LCD) L33640 Biomarkers Overview. Code 81257 for hba1/hba2 gene is covered if age less than 65.

**III. DESCRIPTION/BACKGROUND**

Alpha thalassemia represents a group of clinical syndromes characterized by hemolytic anemia of varying severity. Genetic defects in any or all of four alpha globin genes are causative of these syndromes. The diagnosis of alpha thalassemia is made by biochemical testing and microscopic analysis of the peripheral blood smear. Genetic testing can elucidate the precise number and type of genetic mutations in a patient with a clinical diagnosis of alpha thalassemia. This policy will evaluate genetic testing for confirming a diagnosis of alpha thalassemia and for preconception (carrier) testing. Prenatal (in utero) testing is not addressed in this policy.
Hemoglobin, which is the major oxygen carrying protein molecule of red blood cells, consists of two alpha globin chains and two beta globin chains. Alpha-thalassemia refers to a group of syndromes that arise from deficient production of alpha globin chains. Deficient alpha globin production leads to an excess of beta globin chains, which results in anemia by a number of mechanisms (1):

- Ineffective erythropoiesis in the bone marrow.
- Production of nonfunctional hemoglobin molecules.
- Shortened survival of red blood cells due to intravascular hemolysis and increased uptake of the abnormal red blood cells (RBCs) by the liver and spleen.

The physiologic basis of alpha thalassemia is a genetic defect in the genes coding for alpha globin production. Each individual carries four genes that code for alpha globin, with the wild genotype (normal) being aa/aa. Genetic mutations may occur in any or all of these four alpha globin genes. The number of genetic mutations determines the phenotype and severity of the alpha thalassemia syndromes. The different syndromes are classified as follows:

- **Silent carrier (alpha-thalassemia minima)**. This arises from one of four abnormal alpha genes (aa/a-), 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 (alpha-thalassemia minor)**. This is also called alpha-thalassemia trait, and arises from the loss of two alpha globin genes, resulting on one of two genotypes (aa/--, or a--/a-). There is a mild anemia present, and red blood cells are hypochromic and microcytic. Clinical symptoms are usually absent and the disorder is detected by Hgb electrophoresis and microscopic examination of peripheral RBCs.

- **Hemoglobin H disease (HgH, alpha-thalassemia intermedia)**. This syndrome results from three abnormal alpha globin genes (a-/--), resulting in a moderate to severe anemia. This condition has marked phenotypic variability, but the majority of individuals have mild disease and live a normal life without medical intervention. (2) A minority of individuals may develop clinical symptoms of chronic hemolytic anemia. These 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 HgH disease will require transfusion support during their lifetime. (3) In addition, increased iron deposition can lead to premature damage to the liver and heart.

- **Hemoglobin Bart syndrome (alpha thalassemia major)**. This syndrome results from mutations in all four alpha globin genes (---/--), resulting in absent production of alpha globin chains. This condition causes hydrops fetalis, which often leads to intrauterine death, or death shortly after birth. There are also increased complications of pregnancy for a woman carrying a fetus with hydrops fetalis. These include hypertension, preeclampsia, antepartum hemorrhage, renal failure, premature labor, and abruption placenta.(3)
Alpha thalassemia is a common genetic disorder, affecting approximately 5% of the world’s population. The frequency of mutations is highly dependent upon 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. In contrast, for individuals of northern European ancestry, the carrier rate is less than 1 in 1,000.

Genetic testing

A number of different types of genetic abnormalities are associated with alpha-thalassemia. More than one hundred different genetic mutations have been described. Deletion of one or more of the alpha globin chains is the most common genetic defect. This is the type of genetic defect found in approximately 90% of cases. 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 alpha genes can occur that impair transcription and/or translation of the alpha globin chains.

Testing is commercially available through several genetic labs. The test is most commonly been performed by polymerase chain reaction (PCR), which detects genetic deletions associated with thalassemia. Newer testing methods have been developed to facilitate identification of alpha thalassemia mutations, such as multiplex amplification methods and real-time PCR analysis. In patients with suspected alpha-thalassemia and a negative PCR test for genetic deletions, direct sequence analysis of the alpha-globin locus is generally performed to detect point mutations.

Regulatory Status

Genetic testing for alpha thalassemia is available as a laboratory-developed service, subject only to the general laboratory operational regulation under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. Laboratories performing clinical tests must be certified for high-complexity testing under CLIA. The U.S. Food and Drug Administration (FDA) has not regulated these tests to date.

IV. RATIONALE

This policy was created in August 2013, with review a MEDLINE review of the literature through July 15th 2013. The published literature on genetic testing for alpha thalassemia consists primarily of reports describing the molecular genetics of testing, the types of mutations encountered, and genotype-phenotype correlations. (5-11)
Analytic validity

No published literature was identified on the analytic validity of genetic screening. Some information on the analytic validity of testing was identified from genetic laboratory testing sites. For example, one site reports that “rare” polymorphisms can cause false-negative or false-positive results on gene sequence analysis. (4)

Clinical Validity

No published literature was identified on the clinical validity of genetic screening. Clinical validity is expected to be high when the causative mutation is a large deletion of one or more alpha globin gene, as PCR testing is generally considered highly accurate for this purpose. When a point mutation is present, the clinical validity is less certain.

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 alpha thalassemia. It can also be used to define the genetics of alpha globin genes in relatives of patients with a clinical diagnosis of alpha thalassemia. Preconception (carrier) testing can be performed to determine the likelihood of an offspring with an alpha thalassemia syndrome. Prenatal (in utero) testing can also be performed to determine the presence and type of alpha thalassemia of a fetus. Prenatal testing will not be addressed in this policy.

Confirmation of diagnosis. The diagnosis of alpha thalassemia can be made without use of genetic testing. This is first done by analysis of 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 alpha thalassemia.

Hemoglobin electrophoresis can distinguish between the asymptomatic carrier states and alpha thalassemia intermedia (HgH disease) by identifying the types and amounts of abnormal hemoglobin present. In the carrier states, >95% of the Hb molecules are normal (HbA) with a small minority of HgBA2 present (1-3%). (2) Alpha thalassemia intermedia is diagnosed by finding a substantial portion of HgbH (1-30%) on electrophoresis. (2) In alpha thalassemia major, the majority of the Hgb is abnormal, in the form of Hgb Bart (85-90%). (2) However, biochemical testing cannot always reliably distinguish between the asymptomatic carrier state and alpha thalassemia trait. Genetic testing can differentiate between the asymptomatic carrier state (alpha thalassemia minima) and alpha thalassemia trait (alpha thalassemia minor) by elucidating the number of abnormal genes present. This distinction is not important clinically since both the carrier state and alpha thalassemia trait are asymptomatic conditions that do not require medical care. Since the diagnosis of clinically relevant alpha
thalassemia conditions can be done 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.

Preconception (carrier) testing. The major benefit of carrier testing is to define the likelihood of alpha thalassemia major. Avoiding a pregnancy with alpha thalassemia major is of benefit in that a prospective mother will avoid carrying a non-viable pregnancy, and will avoid the increased obstetrical complications associated with a fetus with alpha thalassemia major. Carrier screening with biochemical testing is recommended for all patients who are from an ethnic groups with a high incidence of alpha thalassemia. Biochemical screening consists of a CBC with peripheral smear analysis. If there are any abnormalities noted, such as anemia, microcytosis, or hypochromia, Hgb electrophoresis is then performed, Hgb electrophoresis will identify the specific types of Hgb present and distinguish between HgH disease and the asymptomatic carrier and trait syndromes.

Unlike for a clinical diagnosis, for carrier testing it is important to distinguish between alpha thalassemia carrier (1 abnormal gene) and alpha thalassemia trait (2 abnormal genes), and also important to distinguish between the two variants of alpha thalassemia trait, that is the aa/-- (cis variant) and the a-/a- (trans variant). This is because only when both parents have the aa/-- cis variant is there a risk for a fetus with alpha thalassemia major. When both parents are alpha thalassemia carriers (aa/-- ), there is a 1 in 4 likelihood that an offspring will have alpha thalassemia major and hydrops fetalis. These parents may decide to pursue pre-implantation 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 HgH 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 Hgb Bart fetus cannot be accurately assessed. In contrast, genetic testing can delineate the number of abnormal genes with certainty. In addition, genetic testing can determine whether alpha thalassemia trait exists as the cis (aa/-- ) variant or the trans (a-/a-) variant. Using this information from genetic testing, the probability of Hgb Bart syndrome can be determined according to the following table:
Parents can also determine the likelihood of HgbH disease in an offspring through genetic testing. However, since this is a relatively mild condition, it is not generally considered information that is actionable in terms of altering reproductive decision making. (12)

**Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**
None

**Summary**

Mutations in the alpha thalassemia gene are common in certain ethnic groups. A variety of alpha thalassemia syndromes can occur, with severity determined by the number of abnormal genes present in an individual. The diagnosis of alpha thalassemia can be made clinically, and the thalassemia syndromes that have clinical implications (HgbBH disease, Hg Bart’s) can be diagnosed biochemically without the need for genetic testing. As a result, genetic testing for confirmation of the diagnosis of alpha thalassemia is considered not medically necessary. Preconception (carrier) testing is intended to avoid the most serious form of alpha thalassemia, Hgb Bart’s disease. 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, but these tests cannot reliably distinguish between the carrier and trait syndromes, and therefore cannot completely determine the risk of a pregnancy with Hg Bart’s syndrome 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. Therefore, genetic testing may be considered medically necessary for carrier screening in parents who screen positive for thalassemia on biochemical tests.
Practice Guidelines and Position Statements

The Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) published guidelines on carrier testing for thalassemia in 2008. (12) These guidelines included the following recommendations:

- Carrier screening for alpha thalassemia should be offered to all women from ethnic groups with an increased prevalence of alpha-thalassemia. Initial screening should consist of CBC, Hgb electrophoresis (or hemoglobin high performance liquid chromatography), ferritin testing and examination of peripheral smear for the presence of H bodies.
- If a woman is found to have abnormal results on initial screen, testing of the partner should be performed using the same battery of tests.
- If both partners are found to be carriers of thalassemia, or combination of a thalassemia and 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.

V. DEFINITIONS

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.
VIII. CODING INFORMATION

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.

Not medically necessary:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81257</td>
<td></td>
</tr>
<tr>
<td>81404</td>
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IX. REFERENCES

MEDICAL POLICY

<table>
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</table>


Other sources

1. Novitas Solutions. Local Coverage Determination (LCD) Biomarkers Overview (L33640)
   Effective 12/05/13. Accessed 12/11/13

X. POLICY HISTORY


Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.