

## Corporate Medical Policy

### Genetic Testing for Alpha Thalassemia AHS – M2131

**File Name:** genetic\_testing\_for\_alpha\_thalassemia  
**Origination:** 01/01/2019  
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#### Description of Procedure or Service

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Alpha-thalassemia is characterized by impaired production of the alpha globin chains of hemoglobin, leading to a relative excess of gamma globin chains (fetus and newborn), or excess beta globin chains (children and adults) mainly due to deletion or mutation of the alpha globin genes. There are four alpha thalassemia syndromes, reflecting the loss of function of one, two, three, or all four of these alpha chain genes varying in severity from non-symptomatic to incompatibility with extrauterine life (Benz, 2017a; Martin & Thompson, 2013).

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

#### Policy

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**BCBSNC will provide coverage for genetic testing for alpha thalassemia when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

#### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

#### When Genetic Testing for Alpha Thalassemia is covered

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1. Preconception (carrier) testing for alpha thalassemia in prospective parents is considered medically necessary when both parents have evidence of possible alpha thalassemia (including alpha thalassemia minor, hemoglobin H disease [alpha thalassemia intermedia], or alpha thalassemia major) based on biochemical testing.
2. Genetic testing to confirm a diagnosis of alpha thalassemia is considered medically necessary when one of the parents is a known carrier or when other testing to diagnose cause of microcytic anemia has been inconclusive (e.g. failure of response to iron therapy) to prevent further unnecessary treatment or testing.

#### When Genetic Testing for Alpha Thalassemia is not covered

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

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## Policy Guidelines

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### Literature Review

Thalassemias result from deficiencies in hemoglobin biosynthesis due to mutations in or near the two globin gene clusters which encode the globin polypeptide subunits of hemoglobin (Benz, 2017a). Normal hemoglobin is a heterotetramer of two alpha globin chains and two beta globin chains (hemoglobin A) or two gamma globin chains (hemoglobin F). Well over 100 mutations have been documented to affect the biosynthesis or post-translational stability of the globin subunits needed for successful production of the large amounts of Hb needed for normal red cell homeostasis (Benz, 2017b). Globin chain synthesis is very tightly controlled, such that the ratio of production of alpha to non-alpha chains is almost exactly 1:1.

Alpha thalassemia refers to thalassemias that result from impaired or absent production of alpha globin, leading to a relative excess of gamma globin (fetus and newborn), or excess beta globin (children and adults). Excess beta globin chains are capable of forming soluble homotetramers, however they are nonfunctional, unstable and are subject to oxidation and precipitation, leading to increased hemolysis and a variety of clinical manifestations (Benz, 2017b).

The majority of cases of alpha thalassemia are attributable to deletion of alpha globin alleles, especially in Asia and Africa (Steinberg, 1999). However, more detailed analysis of globin gene sequences suggests that some fairly common forms of alpha thalassemia that appear to arise from a deletion of one copy of an alpha globin gene are actually due to unequal crossover and recombination events that fuse the two alpha globin genes together into one (Kulozik et al., 1987). Additionally, non-deletion alleles are also common, especially in the Mediterranean area, which contain mutations producing highly unstable alpha globin variants unable to produce intact hemoglobin (Benz, 2017a). Current research continues to identify novel mutations and improve thalassemia screening (He et al., 2018).

There are four alpha thalassemia syndromes of varying clinical severity, reflecting the loss of one, two, three, or all four alpha chain genes (Landaw, 2017) (figure from Landaw)

Disorder	Genotype	MCV	Anemia	Hemoglobin electrophoresis
<b>Alpha thalassemia</b>				
Silent carrier (minima)	$\alpha\alpha / \alpha-$	NL	None	Normal <3% Hb Barts at birth
Minor	$\alpha\alpha / --$ or $\alpha- / \alpha-$	Low	Mild	Normal 3 to 8% Hb Barts at birth
Hb H disease (deletional)	$\alpha- / --$	Low	Moderate	5 to 30% HbH present in adults 20 to 40% Hb Barts at birth
Major (fetal hydrops)	$-- / --$	Low	Fatal	Hb Barts, Hb Portland, and HbH present HbA, HbF, and HbA2 are absent

The clinical severity is directly attributable to the net deficit of alpha globin synthesis, but is complicated by the number of alpha globin genes affected, which of the two alpha globin loci is affected, and the degree to which the mutation blocks gene expression. In addition, combinations of defects in both alpha and beta globulins can balance each other out. Thus, understanding the

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broad spectrum of clinical severity in alpha thalassemia requires a detailed knowledge of the underlying genetic defect and the impact of these defects on the overall levels and balance of globin chain synthesis (Schrier, 2017).

## **Analytical and Clinical Validity**

There is no published evidence on the analytic validity and clinical validity of genetic testing for alpha thalassemia. However, alpha and beta globin gene clusters are small and compact, such that molecular analysis of them at the sequence level is readily performed (Benz, 2017b).

## **Clinical Utility**

There is very limited clinical utility in genetic testing for confirming the clinical diagnosis of alpha thalassemia. Similarly, there is no evidence that genetic testing to assess prognosis of hemoglobin H disease results in changes to patient management or outcomes. Hence, genetic testing for alpha thalassemia is not recommended in these two situations.

There are certain situations such as preconception (carrier) testing in which genetic testing has clinical utility. Carrier testing in parents provides incremental value over biochemical testing and provides a more accurate assessment of the risk of hemoglobin Bart disease and hydrops fetalis. According to Galanello and Cao (Galanello & Cao, 2011), “genetic counseling in alpha-thalassemia is particularly relevant for couples where both partners are alpha carriers, as they are at risk (25%) of their offspring having Hb Bart hydrops fetalis syndrome. For this condition, prenatal diagnosis is always indicated not only for its severity and absence of an effective treatment but also to avoid the severe maternal toxemic complications during pregnancy.” Origa and Moi (Origa & Moi, 2016), state that “family members, members of ethnic groups at risk, and gamete donors should be considered for carrier testing”. They further recommend that “prenatal testing may be carried out for couples who are at high risk of having a fetus with Hb Bart syndrome or for a pregnancy in which one parent is a known  $\alpha$ -thalassemia carrier with a two-gene deletion *in cis* ( $--/\alpha\alpha$ ) when the other parent is either unknown or unavailable for testing” (Origa & Moi, 2016).

Fogel et al (Fogel, Nguyen, Smink, & Sekhar, 2018) published an inventory of state-based recommendations for follow up of the incidental finding of alpha thalassemia carrier or trait identified on newborn screen. They synthesized these guidelines to produce the following standardized recommendation: “for an asymptomatic infant with alpha thalassemia silent carrier or trait, routine health care for the infant without additional testing is appropriate, with the caveat that knowledge of a thalassemia syndrome might influence the evaluation of physical or laboratory abnormalities detected later in infancy or childhood, including jaundice, splenomegaly, or anemia. We would further suggest that targeted screening of the parents, beginning with evaluation for microcytosis, is appropriate to identify families at risk for future children with Hb H disease or hydrops fetalis. For parents with microcytosis, subsequent evaluation should include evaluation of iron status and may be followed by specific molecular testing that would reveal details about deletional and the common nondeletional alpha globin defects.”

## **Applicable Federal Regulations**

Genetic testing for alpha thalassemia is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

## **Guidelines and Recommendations**

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## Practice Guidelines and Position Statements

The Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists (CCMG) and the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) published guidelines on carrier testing for thalassemia in 2008. The guidelines included the following recommendations (Langlois et al., 2008):

- “Carrier screening for thalassemia and hemoglobinopathies should be offered to a woman if she and/or her partner are identified as belonging to an ethnic population whose members are at higher risk of being carriers. Ideally, this screening should be done pre-conceptionally or as early as possible in the pregnancy.”
- “If both partners are found to be carriers of thalassemia or an Hb variant, or of a combination of thalassemia and a hemoglobin variant, they should be referred for genetic counselling. Ideally, this should be prior to conception, or as early as possible in the pregnancy. Additional molecular studies may be required to clarify the carrier status of the parents and thus the risk to the fetus.”
- “Prenatal diagnosis should be offered to the pregnant woman/couple at risk for having a fetus affected with a clinically significant thalassemia or hemoglobinopathy. Prenatal diagnosis should be performed with the patient's informed consent. If prenatal diagnosis is declined, testing of the child should be done to allow early diagnosis and referral to a pediatric hematology centre, if indicated.”

## The Thalassemia Longitudinal Cohort

The report on the Thalassemia Longitudinal Cohort (Tubman et al., 2015) recommends: “Obtaining genotyping to confirm the diagnosis and HLA typing for transplant evaluation for all patients who require chronic transfusion is strongly recommended. For pediatric patients, annual comprehensive follow up should include assessment of the availability of a related donor as well as a recommendation to bank cord blood and obtain HLA typing on all subsequently born full siblings.”

## American College of Obstetrics and Gynecology

The ACOG Committee Opinion #691 states that (ACOG, 2018): “Couples at risk of having a child with a hemoglobinopathy may benefit from genetic counseling to review their risk, the natural history of these disorders, prospects for treatment and cure, availability of prenatal genetic testing, and reproductive options. Prenatal diagnostic testing for the mutation responsible for sickle cell disease is widely available. Testing for  $\alpha$ -thalassemia and  $\beta$ -thalassemia is possible if the mutations and deletions have been previously identified in both parents. These DNA-based tests can be performed using chorionic villi obtained by chorionic villus sampling or using cultured amniotic fluid cells obtained by amniocentesis. For some couples, preimplantation genetic diagnosis in combination with in vitro fertilization may be a desirable alternative to avoid termination of an affected pregnancy. Preimplantation genetic diagnosis has been successfully performed for sickle cell disease and most types of  $\beta$ -thalassemia.

## The Association of Public Health Laboratories (APHL)

Molecular testing (APHL, 2015) can be added to resolve cases when the newborn has been transfused with packed red blood cells. Since the newborn's phenotype is masked by the donor, DNA testing can be used to identify any abnormal hemoglobin.

## Policy Guidelines

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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:

Clinical diagnosis in parents	Genotype (parent 1)	Genotype (parent 2)	Probability of HgB Bart syndrome
Both parents silent carriers	aa/a-	aa/a-	0 percent
One parent silent carrier, one parent trait	aa/a-	a-/a-	0 percent
		aa/a--	0 percent
Both parents trait	aa/--	aa/--	25 percent
		a-/a-	0 percent
	a-/a-	aa/--	0 percent
		a-/a-	0 percent
One parent HgH, one parent silent carrier	a/--	aa/a-	0 percent
One parent HgbH, one parent trait	a/--	aa/--	25 percent
		a-/a-	0 percent
Both parents HgH	a/--	a/--	25 percent

### Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81257, 81258, 81259, 81269*

Code Number	PA Required	PA Not Required	Not Covered
81257	X		
81258	X		
81259	X		
81269	X		

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

### Scientific Background and Reference Sources

ACOG. (2018). ACOG Committee Opinion 691; Carrier Screening for Genetic Conditions - ACOG. (1074-861X). <https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Genetics/Carrier-Screening-for-Genetic-Conditions>

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## Policy Implementation/Update Information

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1/1/2019 BCBSNC will provide coverage for genetic testing for alpha thalassemia when it is determined to be medically necessary because the criteria and guidelines are met. Medical Director review 1/1/2019. (jd)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational

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purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.