

Test Specific Guidelines



Hemoglobinopathies Genetic Testing

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Introduction

Testing for hemoglobinopathies is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
HBA1/HBA2 Targeted Mutation Analysis	<u>81257</u>
HBA1/HBA2 Known Familial Mutation Analysis	<u>81258</u>
HBA1/HBA2 Sequencing	<u>81259</u>
HBA1/HBA2 Deletion/Duplication Analysis	<u>81269</u>
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What Are Hemoglobinopathies?

Definition

Hemoglobinopathies are a group of genetic disorders involving abnormal production or structure of the hemoglobin protein.¹

Hemoglobin is found in red blood cells and is responsible for delivering oxygen throughout the body. It is composed of four polypeptide sub-units (globin chains) that normally associate with each other in one of the following forms:

Hemoglobin A (HbA), composed of two alpha and two beta chains, makes up about 95-98% of adult hemoglobin.



<u>Hemoglobin A₂ (HbA₂), composed of two alpha and two delta chains, makes up about 2-3% of adult hemoglobin.</u>

Hemoglobin F (HbF, fetal hemoglobin), composed of two alpha and two gamma chains, makes up about 1-2% of adult hemoglobin.

While there is only one beta globin gene (HBB), there are 2 different genes that code for alpha globin: HBA1 and HBA2. Thus, humans have 4 alpha globin gene copies (two from each parent) and 2 beta globin gene copies (one from each parent).

More than one thousand hemoglobin variants have been discovered to date.¹ Although most do not cause disease, some variants affect the size, shape, and efficacy of red blood cells.^{2,3}

Incidence and Prevalence

As a group, hemoglobinopathies constitute the most common single-gene disease in the world. Approximately 7% of the world's population carries a mutation associated with a hemoglobinopathy.³ Ethnic-specific carrier rates for various hemoglobinopathies appear in the table below.⁴ Although hemoglobinopathies are more common in certain ethnic groups, they have been described in populations worldwide.

<u>Ethnicity</u>	<u>Beta Thalassemia</u> <u>trait</u>	Alpha thalassemia trait (cis vs trans)*	<u>Sickle cell trait</u>
<u>Mediterranean</u>	<u>1/20 - 1/30</u>	<u> 1/30 - 1/50 (trans)</u>	<u>1/30 - 1/50</u>
African American	<u>1/75</u>	<u>1/30 (trans)</u>	<u>1/12</u>
West African	<u>1/50</u>	<u>1/30 (trans)</u>	<u>1/6</u>
<u>Non-Hispanic</u> Caribbean, West Indian	<u>1/50 - 1/75</u>	<u>1/30 (trans)</u>	<u>1/12</u>
<u>Hispanic</u> Caribbean	<u>1/75</u>	<u>Variable</u>	<u>1/30</u>
<u>Hispanic Latin</u> <u>American</u>	<u>1/30 - 1/50</u>	<u>Variable</u>	<u>1/30 - 1/200</u>
Southeast Asian	<u>1/30</u>	<u>>1/20 (cis)</u>	Rare
South Asian	<u>1/30 - 1/50</u>	<u>Variable</u>	<u>1/50-1/100</u>
Other Asian	<u>1/50</u>	>1/20	Rare
Middle Eastern	<u>1/50</u>	<u>Variable</u>	<u>1/50-1/100</u>

Ethnic-specific Carrier Rates for Various Hemoglobinopathies



Note * The clinically significant carrier state of alpha thalassemia is defined as the absence or dysfunction of two copies of the HBA genes. If both non-working copies are on the same chromosome, the mutations are referred to as being in 'cis'. If there is one gene from each chromosome affected, the mutations are referred to as being in 'trans'.

Symptoms

Most cases of hemoglobinopathies in the US are diagnosed through newborn screening prior to symptom onset.² The exception is the severe form of alpha thalassemia (Hb Bart syndrome), which has prenatal onset and can cause fetal or neonatal death.

Alpha thalassemia: Hb Bart syndrome (absence of all 4 alpha globin genes) presents as general fetal edema, pleural and pericardial effusion, and severe anemia.^{4,5} HbH disease (absence of 3 of the 4 alpha globin genes) presents postnatally with anemia, enlarged spleen, and mild jaundice.⁵

Beta thalassemia: Untreated severe beta-thalassemia (beta⁰-thalassemia, or beta thalassemia major) can present as failure to thrive with an enlarged liver and spleen.⁶ Milder forms of the disease (Beta⁺ thalassemia or beta thalassemia intermedia) present later in life with milder anemia.⁶ Very mild forms of beta thalassemia can be clinically asymptomatic.

Sickle cell disease: Untreated sickle cell disease presents as hemolytic anemia, vaso-occlusive events, and swelling of the hands and feet.⁷

<u>Carriers of hemoglobinopathies are usually clinically asymptomatic but typically</u> <u>have subclinical microcytic anemia (abnormal blood indices).</u>

<u>Cause</u>

Thalassemias are typically caused by mutations in globin chain genes that result in reduced or absent synthesis of a normal protein product. Structural hemoglobin variants are caused by mutations in globin chain genes that result in synthesis of normal quantities of an abnormal protein product.

Alpha thalassemia is caused by loss of function mutations in the HBA1 or HBA2 genes. Gene deletions are the most common causative mutations.⁵ Of nondeletion mutations, the point mutation Hb Constant Spring (HbCS) is the most common and may be clinically more severe than a deletion mutation; this mutation is most common in Southeast Asians.⁵ Symptoms occur when at least 3 of the 4 alpha globin genes are mutated. If 1 or 2 genes are mutated, the individual is asymptomatic and considered a carrier of alpha thalassemia.

Beta thalassemia is caused by loss of function mutations in the HBB gene. Nonsense, small frameshift, and splice site mutations are the most common causative mutations, and gene deletions are rare. In general, beta⁰ thalassemias are due to complete loss of the beta globin protein, while beta⁺ thalassemias are due to decreased production of beta globin.⁶

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HbS (sickle hemoglobin) is caused by a single HBB mutation (p.Glu6Val).⁵ Similarly, HbC (p.Glu6Lys) and HbE (p.Glu26Lys) are also caused by single HBB mutations. Other structural hemoglobin variants are grouped according to electrophoretic properties (HbD, HbG) but have multiple subtypes caused by different mutations, potentially in different hemoglobin chain-coding genes.¹

<u>Structural hemoglobin variants can be co-inherited with one another or with alpha</u> or beta thalassemia deletions/mutations. These combinations can result in a wide range of phenotypes, dependent upon both the specific structural variant and thalassemia mutation.⁶

Inheritance

Most hemoglobinopathies are inherited in an autosomal recessive manner.^{5,6}

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Carriers of beta thalassemia mutations and the HbS structural variant are often referred to as having thalassemia trait or sickle cell trait. As there are 2 different alpha globin genes (HBA1 and HBA2), the mutation of 2 of the 4 four genes is required to be considered a carrier (alpha thalassemia trait). The mutation of 1 of the 4 alpha globin genes is often referred to as silent carrier state.

<u>Diagnosis</u>

Hemoglobinopathies are generally diagnosed based on clinical presentation and/or hematologic laboratory analysis.^{5,6} These tests include:

<u>Complete blood count (CBC): mean corpuscular volume (MCV) and mean</u> <u>corpuscular hemoglobin (MCH) are measures of red cell size, and, together with</u> <u>decreased red blood cells, diagnose microcytic anemia. MCV and MCH are</u> <u>usually decreased in thalassemias.</u>

Hemoglobin electrophoresis, isoeletric focusing (IEF) and high performance liquid chromatography (HPLC) detect and quantify hemoglobin subtypes, identifying structural hemoglobin variants and detecting abnormal levels of normal adult hemoglobin.¹ In beta thalassemia, HbA₂ and HbF are usually increased.⁶ Exclusion of iron deficiency as a cause of microcytic anemia via serum iron concentration, ferritin, transferrin and/or total iron binding capacity assessment.

<u>Molecular testing is not generally required for diagnosis or management</u> <u>purposes, but may be indicated if the hematologic results are inconclusive, when</u> <u>molecular findings would impact medical management, or to identify familial</u> <u>mutations for reproductive planning purposes.^{5,6}</u>

<u>Management</u>

Hemoglobinopathies are treated with packed red cell transfusions as needed.⁵⁻⁷ Iron chelation therapy helps prevent iron overload in individuals receiving regular transfusions.^{5,6} Individuals with sickle cell disease may also be treated with hydroxyurea to increase production of fetal hemoglobin.⁹ For individuals with severe beta-thalassemia or sickle cell disease, stem cell/bone marrow transplant may be considered.^{6,7}

Test Information

Introduction

Diagnostic testing for hemoglobinopathies is generally based on clinical findings, red blood cell indices (MCV and MCH) and results of quantitative hemoglobin electrophoresis and other protein-based analyses of hemoglobin. Genetic testing for hemoglobinopathies consists of targeted mutation analysis, sequencing, deletion/duplication analysis, and known familial mutation testing.

HBA1 and HBA2 Genetic Testing

Genetic testing for hemoglobinopathies caused by mutations of alpha globin genes HBA1 and HBA2 may include a common mutation panel, gene sequencing, deletion/duplication analysis, or known familial mutation analysis.

HBA1 and HBA2 targeted mutation analysis

About 90% of pathogenic HBA1 and HBA2 mutations can be identified by a targeted panel of common deletions. Detection rates depend on ethnicity.⁴ The most common deletions are - a^{3.7}, - a^{4.2}, and -a^{20.5} (single gene deletions), and – SEA, -MED, –FIL, and –THAI (two gene deletions). These deletions are most commonly found in the Southeast Asian, African, Middle Eastern, West Indian, and Mediterranean populations.⁵ Some common mutation panels also include the point mutation, Hb Constant Spring.

HBA1 and HBA2 sequencing

If common deletion testing for HBA1 and HBA2 is negative or does not find the expected number of mutations, sequencing of the HBA1 and HBA2 genes can then be performed to identify point mutations, small indels, or splice mutations.⁵



HBA1 and HBA2 deletion/duplication analysis

When no common mutation has been identified by a targeted panel, full deletion/duplication analysis of the HBA1/HBA2 locus may be indicated; such analysis identifies mutations in fewer than 5% of patients.⁵ Some labs perform this type of assessment instead of a targeted deletion panel. Deletion/duplication analysis, however, should be performed if a gene triplication or other copy number variation is suspected based on phenotype, as this would not be detected on a common mutation panel.

HBA1 and HBA2 known familial mutation analysis

This test looks specifically for known deletion(s)/mutation(s) previously identified in the family. This may be accomplished through a targeted assessment of the specific familial mutation or a common deletion panel.

HBB Genetic Testing

<u>Genetic testing for hemoglobinopathies caused by mutations of the beta globin</u> <u>gene HBB may include targeted mutation analysis, gene sequencing,</u> <u>deletion/duplication analysis, or known familial mutation analysis.</u>

HBB targeted mutation analysis

<u>Targeted HBB mutation panels can consist of a few of the most common</u> <u>structural hemoglobin variants and beta-thalassemia associated mutations or</u> <u>dozens of reported mutations across ethnicities.^{6,7} Clinical sensitivity of a</u> <u>panel depends on patient ethnicity, hematologic test results, and the</u> <u>mutations included on the panel.</u>

HBB sequencing

Full HBB gene sequencing identifies >99% of mutations in the coding region, including the common HbS and beta thalassemia mutations.^{6,7}

HBB deletion/duplication analysis

Beta thalassemia caused by pathogenic HBB deletions or duplications is rare, but has been reported.⁶

HBB known familial mutation analysis

This test looks specifically for known mutation previously identified in the family. This may be accomplished through a targeted assessment of the specific familial mutation(s) or a common mutation panel.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to hemoglobinopathy testing.



American College of Obstetricians and Gynecologists

Evidence-based guidelines from American College of Obstetricians and Gynecologists (ACOG, 2007) recommend that couples at risk of having a child with a hemoglobinopathy be offered prenatal diagnostic options including amniocentesis or chorionic villus sampling (CVS) (level A recommendation: based on "good and consistent scientific evidence").⁸ Identification of parental mutations should be performed before prenatal diagnosis to inform interpretation of prenatal results.⁸

ACOG Committee Opinion 690 (2020) stated that all patients considering pregnancy or already pregnant, regardless of screening strategy and ethnicity, should be offered complete blood count and screening for hemoglobinopathy.⁹

ACOG Committee Opinion 691 (2017) expanded on recommended screening methodology: All pregnant women should have a complete blood count with red cell indices. For women of high-risk ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian and West Indian), hemoglobin electrophoresis should also be performed. For all other women, hemoglobin electrophoresis is recommended only if red cell indices indicate low mean MCH or MCV.¹⁰

British Committee for Standards in Haematology

The British Committee for Standards in Haematology (BCSH, 2010) issued a comprehensive guideline for postnatal screening and diagnosis of hemoglobinopathies.¹¹ The guideline included indications for DNA analysis, noting that "the identification of haemoglobins is often presumptive, based on electrophoretic mobility or other characteristics in an individual of appropriate family origin. Presumptive identification should be based on a minimum of two techniques based on different principles. Definitive identification usually requires DNA analysis, mass spectrometry or protein sequencing."

"The majority of couples at risk of having a child affected with b-thalassaemia or SCD should be identified initially by routine laboratory techniques through the antenatal screening programme. The diagnosis of α -thalassaemia is more complicated because DNA analysis is the only accurate way to distinguish between α^+ and α^0 thalassaemia. However it is not practical to seek to confirm all potential cases of α -thalassaemia by DNA analysis because the α^+ form is too common and not usually clinically important."

Society of Obstetricians and Gynaecologists of Canada

Evidence-based guidelines from the Society of Obstetricians and Gynaecologists of Canada (SOGC, 2016) stated the following regarding screening for thalassemia and other hemoglobinopathies.¹²

"Carrier screening for hemoglobinopathies should be offered to women/families from ethnic backgrounds with a reported increased carrier frequency, when red blood cell indices reveal a mean cellular volume < 80 fl, or electrophoresis reveals an abnormal hemoglobin type. However, the use of ethnicity alone in the carrier risk identification process may create screening inconsistency and missed opportunity for carrier identification, with both obstetrical and fetal implications. High clinical suspicion is required as well. Screening should be done in the preconception period or as early into the pregnancy as possible. (II-2A) (GRADE moderate/moderate)"

<u>"Carrier screening for thalassemia/hemoglobinopathies should be offered by the most responsible health care provider or reproductive genetic provider and include:"</u>

"Complete blood count"

<u>"Hemoglobin (Hb) electrophoresis (HE) or Hb high performance liquid chromatography (HHPLC)</u>"

"Quantification of Hb alpha 2 and fetal Hb"

<u>"Serum ferritin/H bodies (blood smear stain using brilliant cresyl blue) if</u> microcytosis (mean cellular volume < 80 fl) and/or hypochromia (mean cellular Hb < 27 pg) in the presence of a normal HE or HHPLC assessment. (II-2A) (GRADE moderate/moderate)"

"If the female thalassemia screening results are abnormal, a hemoglobinopathy screening protocol should be undertaken for the male partner. (III-A) (GRADE low/moderate)"

<u>"If both reproductive partners are found to be carriers of thalassemia or a</u> <u>combination of thalassemia and hemoglobin variant, they should be referred for</u> <u>formal genetic counselling (reproductive risks, recommended prenatal testing,</u> <u>and diagnostic management). (II3A) (GRADE moderate/moderate)"</u>

Criteria

Introduction

Requests for hemoglobinopathy testing are reviewed using these criteria.

HBA1 and HBA2 Targeted Mutation Analysis

Genetic Counseling:

<u>Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND</u>

Previous Genetic Testing:

<u>No previous HBA1 or HBA2 targeted mutation testing has been performed, AND</u> <u>Diagnostic Testing for Symptomatic Individuals:</u> <u>Results of hematologic tests examining MCV, MCH, iron deficiency, and hemoglobin electrophoresis do not conclusively diagnose or rule out alpha thalassemia, and</u>

Documentation from ordering provider indicates how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), OR

Carrier Testing:

Member is pregnant or of reproductive age with intention to reproduce, and

Both member and partner meet the following criteria:

MCV and/or MCH lower than reference range of testing lab, and

Hemoglobin electrophoresis is not consistent with beta chain abnormality, and

Iron deficiency anemia has been ruled out, or

<u>Member is currently pregnant and meets above criteria and the father of the</u> pregnancy is not available for testing but believed to be from a high-risk ethnic population, and

Identification of pathogenic familial mutations is required for prenatal diagnosis or pregnancy planning, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

HBA1 and HBA2 Deletion Analysis

Genetic Counseling:

<u>Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND</u>

Previous Genetic Testing:

<u>Previous common mutation panel genetic testing for HBA1 or HBA2 mutations (if performed) was negative, AND</u>

Diagnostic Testing for Symptomatic Individuals:

<u>Results of hematologic tests examining MCV, MCH, iron deficiency, and hemoglobin electrophoresis do not conclusively diagnose or rule out alpha thalassemia, and</u>

Documentation from ordering provider indicates how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), OR

Carrier Testing:

Member is pregnant or of reproductive age with intention to reproduce, and



Both member and partner meet the following criteria:

MCV and/or MCH lower than reference range of testing lab, and

Hemoglobin electrophoresis is not consistent with beta chain abnormality, and

Iron deficiency anemia has been ruled out, or

<u>Member is currently pregnant and meets above criteria and the father of the</u> pregnancy is not available for testing but believed to be from a high-risk ethnic population, and

Identification of pathogenic familial mutations is required for prenatal diagnosis or pregnancy planning, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

HBA1 and HBA2 Sequencing

Genetic Counseling:

<u>Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND</u>

Previous Genetic Testing

Previous common mutation panel or deletion/duplication genetic testing for HBA1 or HBA2 was negative, AND

Diagnostic Testing for Symptomatic Individuals:

Results of hematologic tests examining MCV, MCH, iron deficiency, and hemoglobin electrophoresis do not conclusively diagnose or rule out alpha thalassemia, and

Documentation from ordering provider indicates how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), OR

Carrier Testing:

Member is pregnant or of reproductive age with intention to reproduce, and

Both member and partner meet the following criteria:

MCV and/or MCH lower than reference range of testing lab, and

Hemoglobin electrophoresis is not consistent with beta chain abnormality, and

Iron deficiency anemia has been ruled out, or

Member is pregnant and meets above criteria and the father of the pregnancy is not available for testing but believed to be from a high-risk ethnic population, and

Identification of pathogenic familial mutations is required for prenatal diagnosis or pregnancy planning, AND



Rendering laboratory is a qualified provider of service per the Health Plan policy.

HBA1 and HBA2 Known Familial Mutation Analysis

Genetic Counseling:

<u>Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND</u>

Previous Genetic Testing:

Known familial mutation in HBA1 and/or HBA2 identified in a close blood relative, and

No previous genetic testing for known HBA1 or HBA2 family mutation, AND

Diagnostic Testing for Symptomatic Individuals:

<u>Results of hematologic tests examining MCV, MCH, iron deficiency, and hemoglobin electrophoresis do not conclusively diagnose or rule out alpha thalassemia, and</u>

Documentation from ordering provider indicates how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), OR

Carrier Screening:

Member is pregnant or of reproductive age with intention to reproduce, and

Both member and partner meet the following criteria:

MCV and/or MCH lower than reference range of testing lab, and

Hemoglobin electrophoresis is not consistent with beta chain abnormality, and

Iron deficiency anemia has been ruled out, or

Member is pregnant and meets above criteria and the father of the pregnancy is not available for testing but believed to be from a high-risk ethnic population, and

Identification of pathogenic familial mutations is required for prenatal diagnosis or pregnancy planning, OR

Prenatal Testing:

Both biological parents carry HBA1/HBA2 mutations that put the pregnancy at risk for a clinically significant anemia, or

The pregnant member carries HBA1/HBA2 mutations that put the pregnancy at risk for a clinically significant anemia and the father of the pregnancy is unavailable but believed to be from a high-risk ethnic population, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

HBB Targeted Mutation Analysis

Genetic Counseling:

<u>Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND</u>

Previous Genetic Testing:

No previous genetic testing for HBB mutation, AND

Diagnostic Testing for Symptomatic Individuals:

Results of hematologic tests examining MCV, MCH, iron deficiency, and hemoglobin electrophoresis do not conclusively diagnose or rule out beta thalassemia, or

Hemoglobin electrophoresis shows common structural variant caused by mutation contained on the requested panel (HbS, HbC, HbE, etc), and

Documentation from ordering provider indicates how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), OR

Carrier Testing:

Member is pregnant or of reproductive age with intention to reproduce, and

Both member and partner meet the following criteria:

MCV and/or MCH lower than reference range of testing lab, and

Iron deficiency anemia has been ruled out, and

Hemoglobin electrophoresis shows

elevated Hb A₂ (based on reference range of the testing lab) consistent with beta thalassemia, or

<u>common structural variant caused by mutation contained on the requested panel</u> (HbS, HbC, HbE, etc), or

Member is pregnant and meets above criteria and the father of the pregnancy is not available for testing but believed to be from a high-risk ethnic population, and

Identification of pathogenic familial mutations is required for prenatal diagnosis or pregnancy planning, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

HBB Sequencing

Genetic Counseling:



<u>Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND</u>

Previous Genetic Testing:

Previous HBB targeted mutation analysis (if performed) was negative, or

Individual is not of a high-risk ethnicity for which HBB targeted mutation analysis is available and of high sensitivity, AND

Diagnostic Testing for Symptomatic Individuals:

<u>Results of hematologic tests examining MCV, MCH, iron deficiency, and hemoglobin electrophoresis do not conclusively diagnose or rule out beta thalassemia, or</u>

Hemoglobin electrophoresis shows uncommon structural variant caused by one of several possible HBB mutations, and

Documentation from ordering provider indicates how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), OR

Carrier Testing:

Member is pregnant or of reproductive age with intention to reproduce, and

Both member and partner meet the following criteria:

<u>Results of hematologic tests examining MCV, MCH, iron deficiency, and</u> <u>hemoglobin electrophoresis do not conclusively rule out beta thalassemia, or</u>

Hemoglobin electrophoresis shows uncommon structural variant caused by one of several possible HBB mutations, or

The pregnant member meets above criteria for HBB carrier testing and the father of the pregnancy is unavailable but believed to be from a high-risk ethnic population, and

Identification of pathogenic familial mutations is required for prenatal diagnosis or pregnancy planning, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

HBB Deletion/Duplication Analysis

Genetic Counseling:

<u>Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND</u>

Previous Genetic Testing:

<u>Previous testing via either HBB targeted mutation analysis or HBB full</u> <u>sequencing performed and negative, AND</u> Diagnostic Testing for Symptomatic Individuals:

<u>Results of hematologic tests examining MCV, MCH, iron deficiency, and</u> <u>hemoglobin electrophoresis do not conclusively diagnose or rule out beta</u> <u>thalassemia, and</u>

Documentation from ordering provider indicates how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), OR

Carrier Testing:

Member is pregnant or of reproductive age with intention to reproduce, AND

Both member and partner have

<u>Results of hematologic tests examining MCV, MCH, iron deficiency, and</u> <u>hemoglobin electrophoresis do not conclusively rule out beta thalassemia, or</u>

<u>Hemoglobin electrophoresis shows uncommon structural variant caused by one</u> of several possible HBB mutations, or

The pregnant member meets above criteria for HBB carrier testing and the father of the pregnancy is unavailable but believed to be descended from a high-risk ethnic population, and

Identification of pathogenic familial mutations is required for prenatal diagnosis or pregnancy planning, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy

HBB Known Familial Mutation Analysis

Genetic Counseling:

<u>Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND</u>

Previous Genetic Testing:

Known familial mutation in HBB identified in a close blood relative, and

No previous genetic testing for known HBB family mutation, AND

Diagnostic Testing for Symptomatic Individuals:

<u>Results of hematologic tests examining MCV, MCH, iron deficiency, and</u> <u>hemoglobin electrophoresis do not conclusively rule out beta thalassemia, and</u>

Documentation from ordering provider indicates how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), OR

Carrier Testing:



Member is pregnant or of reproductive age with intention to reproduce, AND

Both member and partner have

<u>Results of hematologic tests examining MCV, MCH, iron deficiency, and</u> <u>hemoglobin electrophoresis do not conclusively rule out beta thalassemia, or</u>

Hemoglobin electrophoresis shows uncommon structural variant caused by one of several possible HBB mutations, or

The pregnant member meets above criteria for HBB carrier testing and the father of the pregnancy is unavailable but believed to be descended from a high-risk ethnic population, and

Identification of pathogenic familial mutations is required for prenatal diagnosis or pregnancy planning, AND

Prenatal Testing

Both biological parents carry HBB mutations that put the pregnancy at risk for a clinically significant anemia, or

The pregnant member carries an HBB mutation that puts the pregnancy at risk for a clinically significant anemia and the father of the pregnancy is unavailable but believed to be from a high-risk ethnic population, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

References

Introduction

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