Preconception Screening for Carrier Status of Genetic Diseases


Effective Date: Oct. 1, 2018
Last Revised: Sept. 20, 2018
Replaces: 12.04.107

RELATED MEDICAL POLICIES:
- 12.04.93 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
- 12.04.519 Genetic Testing for Alpha Thalassemia

Introduction

Genetic tests are laboratory tests that measure changes in human DNA, chromosomes, genes or gene products (proteins). Blood, skin, cheek swabs, and amniotic fluid are some common samples that can be tested. Genetic testing for carrier status is done on people planning a pregnancy. The goal is to see if they have a potential disease that could be passed on to their offspring. For certain disorders, a carrier state can exist where a person has no symptoms of the disease, but has the potential to pass the disease on to their children because they carry a gene for the disease. Often it takes at least two copies of the gene for the disease to cause symptoms. Usually carrier testing is done before conception when individuals are planning a pregnancy, but it may also be done in the early stages of pregnancy.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs providers about when a service may be covered.
Policy Coverage Criteria

This policy applies only if there is not a separate policy that outlines specific criteria for carrier testing. If a separate policy exists, then criteria for medical necessity in that policy supersedes the guidelines in this policy (see Related Policies).

**Note:** Usually carrier testing is done before conception when individuals are planning a pregnancy, but it may also be done in the early stages of pregnancy.

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expanded Carrier</td>
<td><strong>Expanded carrier screening panels which test for mutations on many different genes are considered not medically necessary.</strong> Based on the individual tested, a subset of tests within the panel may be covered when the policy criteria are met.</td>
</tr>
<tr>
<td></td>
<td>The names of expanded carrier panels, and their individual mutation components, are rapidly evolving. Examples of panels addressed in this policy include but are not limited to:</td>
</tr>
<tr>
<td></td>
<td>• Counsyl™ (Counsyl)</td>
</tr>
<tr>
<td></td>
<td>• GoodStart Select™ (GoodStart Genetics)</td>
</tr>
<tr>
<td></td>
<td>• Inherigen™ (GenPath)</td>
</tr>
<tr>
<td></td>
<td>• InheriGen Plus</td>
</tr>
<tr>
<td></td>
<td>• Inheritest™ (LabCorp)</td>
</tr>
<tr>
<td></td>
<td>• Natera One™ Disease Panel (Natera)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetic Disease</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>The General Population</td>
<td><strong>Covered for all individuals with a panel that tests the most common genes</strong></td>
</tr>
<tr>
<td>Cystic fibrosis (CPT 81220)</td>
<td>Note: Carrier testing for cystic fibrosis using CPT 81223 “CFTR (eg, cystic fibrosis) gene analysis; full gene sequence” is considered not medically necessary for carrier testing.</td>
</tr>
</tbody>
</table>
### Genetic Disease Medical Necessity

<table>
<thead>
<tr>
<th>Genetic Disease</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal muscular atrophy (CPT 81400, 81401)</td>
<td>Covered for all individuals</td>
</tr>
</tbody>
</table>

### Specific Groups or Populations

The following genetic testing may also be considered medically necessary due to an increased frequency of certain disorders in groups or populations.

<table>
<thead>
<tr>
<th>Ashkenazi Jewish founder mutations:</th>
<th>Ashkenazi Jewish founder mutations may be considered medically necessary when the individual meets one of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bloom syndrome</td>
<td>• Ashkenazi Jewish ancestry consisting of a minimum of one Jewish grandparent</td>
</tr>
<tr>
<td>• Canavan disease</td>
<td>• If the Jewish partner has a positive carrier test result, the other partner (regardless of ethnic background) should be screened only for that identified mutation</td>
</tr>
<tr>
<td>• Cystic fibrosis</td>
<td>Genetici testing for Ashkenazi Jewish founder mutation is considered not medically necessary for all other uses.</td>
</tr>
<tr>
<td>• Familial dysautonomia</td>
<td></td>
</tr>
<tr>
<td>• Fanconi anemia (group C)</td>
<td></td>
</tr>
<tr>
<td>• Gaucher disease</td>
<td></td>
</tr>
<tr>
<td>• Mucolipidosis IV</td>
<td></td>
</tr>
<tr>
<td>• Niemann-Pick (type A)</td>
<td></td>
</tr>
<tr>
<td>• Tay-Sachs disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FMR1 variants (including Fragile-X syndrome)</th>
<th>Genetic testing for FMR1 variants may be considered medically necessary when any of the following criteria are met:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Parent of either sex with intellectual disability, developmental delay, or autism spectrum disorder</td>
<td>• Parent with a family history of fragile X syndrome or a family history of undiagnosed intellectual disability</td>
</tr>
<tr>
<td>• Parent with a family history of fragile X syndrome or a family history of undiagnosed intellectual disability</td>
<td>• Prenatal testing of fetuses of mothers who are known carriers to determine whether the fetus inherited the normal or mutant FMR1 gene</td>
</tr>
<tr>
<td>• Prenatal testing of fetuses of mothers who are known carriers to determine whether the fetus inherited the normal or mutant FMR1 gene</td>
<td>• Affected individuals or first- and second- degree relatives of affected individuals who have had a positive cytogenetic fragile X test (less accurate historic test) result who are seeking further counseling related to the risk of carrier status</td>
</tr>
</tbody>
</table>

Genetic testing for FMR1 variants (including Fragile-X syndrome) is considered not medically necessary for all other uses.
<table>
<thead>
<tr>
<th>Genetic Disease</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Alpha-thalassemia preconception (carrier) testing** | Preconception (carrier) testing for alpha-thalassemia in prospective parents may be considered medically necessary when all of the following criteria are met:  
• At least one parent is of a high-risk ethnic group, such as Southeast Asian, African or Mediterranean ancestry  
• At least one parent has had abnormal biochemical testing which may include ANY of the following:  
  o Anemia  
  o Microcytosis (a low MCV – small blood cells)  
  o Hypochromia (a low MCH or MCHC – red blood cells with less hemoglobin)  
  o Abnormal hemoglobin electrophoresis  

Genetic testing for hemoglobinopathies, except for alpha-thalassemia, is considered not medically necessary.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| **Other Inherited Disorders**                        | May be considered medically necessary when ONE of the following criteria are present:  
• One or both parents have a first- or second-degree relative* who has the disorder  
• One parent is or both parents are a known carrier of the disorder.  

Note: 1st-degree relatives are parents, siblings, and children. 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.  

AND all of the following criteria must also be met:  
• The natural history of the disease is understood and the disease is likely to result in severe health problems  
• Other biochemical or clinical tests to diagnose carrier status are...
### Genetic Disease | Medical Necessity
---|---
| 
| not available, or are less accurate than genetic testing
- The genetic test has adequate sensitivity and specificity to guide clinical decision making
  - The American College of Medical Genetics and Genomics (ACMG) recommends testing for specific mutations, which will result in carrier detection rate of 95% or higher for most disorders.
- A clear association of the genetic change with the disorder has been established

**Genetic testing for other specific disorders is considered not medically necessary when the criteria above are not met.**

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81257</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring) (effective 1/1/18)</td>
</tr>
<tr>
<td>81258</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant (effective 1/1/18)</td>
</tr>
<tr>
<td>81259</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence (effective 1/1/18)</td>
</tr>
<tr>
<td>81269</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants (effective 1/1/18)</td>
</tr>
<tr>
<td>81412</td>
<td>Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), gene analysis; full gene sequence (effective 1/1/18)</td>
</tr>
</tbody>
</table>
### Related Information

If there is no family history of, risk based or ethnic predilection for a disease, carrier screening is not recommended when the carrier rate is less than 1% in the general population.

ACMG has defined expanded panels as those that use next-generation sequencing to screen for variants in many genes, as opposed to gene-by-gene screening (eg, ethnic-specific screening or pan-ethnic testing for cystic fibrosis).

Expanded panels may include the diseases that are present with increased frequency in specific populations, but typically include testing for a wide range of diseases for which the patient is not at risk of being a carrier.

Carrier screening should only be performed in adults.

For individuals who are at risk due to an established family history of fragile X syndrome, DNA testing alone is sufficient. If the diagnosis of the affected relative was based on previous cytogenetic testing for fragile X syndrome, at least one affected relative should have DNA testing.

Prenatal testing of a fetus should be offered when the mother is a known carrier to determine whether the fetus inherited the normal or mutant FMR1 gene. Ideally DNA testing should be performed on cultured amniocytes obtained by amniocentesis after 15 weeks’ gestation. DNA testing can be performed on chorionic villi obtained by chorionic villus sampling at 10 to 12 weeks’ gestation, but results must be interpreted with caution because the methylation status of the FMR1 gene is often not yet established in chorionic villi at the time of sampling. follow-up amniocentesis may be necessary to resolve an ambiguous result.
Definition of Terms

1st-, 2nd-, or 3rd-degree relative: For the purpose of familial assessment, 1st-, 2nd-, or 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal). The maternal and paternal sides of the family should be considered independently for familial patterns of inherited disorders.

- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins

Carrier testing: Carrier genetic testing is performed on people who display no symptoms for a genetic disorder but may be at risk for passing it on to their children.

A carrier of a genetic disorder has one abnormal allele for a disorder. Carriers of an autosomal recessive mutation are typically unaffected. Offspring who inherit the mutation from both parents usually manifest the disorder. When associated with an autosomal dominant or an X-linked dominant disorder, the individual may be affected with the disorder or be at high risk of developing the disorder later in life. Women with an X-linked recessive mutation are usually unaffected. Males receiving a chromosome with an X-linked recessive mutation usually manifest the disorder.

Compound heterozygous: The presence of two different mutant alleles at a particular gene locus, one on each chromosome of a pair.

Expressivity/expression: The degree to which a penetrant gene is expressed within an individual.

Genetic testing: A test that analyzes chromosomes, DNA, RNA, genes, or gene products to detect inherited (germline) or non-inherited (somatic) genetic variants related to disease or health

Homozygous: Having the same alleles at a particular gene locus on homologous chromosomes (chromosome pairs).

Penetrance: The proportion of individuals with a mutation that causes a particular disorder who exhibit clinical symptoms of that disorder.
Residual risk: The risk that an individual is a carrier of a particular disease, but genetic testing for carrier status of the disease is negative (eg, if the individual has a disease-causing mutation that wasn’t included in the test assay).

Testing sequence: Testing sequence of carrier testing for genetic diseases is generally done on the mother or affected partner first, and if positive, then the other parent is tested.

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 (see Table 1). 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 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant Classification</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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 when genetic testing for an inherited condition is considered. Interpreting the results of genetic tests and understanding 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 substantially alter the utilization of genetic testing and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Evidence Review**

**Description**

Carrier screening is performed to identify individuals at risk of having offspring with inherited single-gene disorders. Carriers are usually not at risk of developing the disease, but can pass pathogenic variants to their offspring. Carrier testing may be performed in the prenatal or preconception periods.
Background

Inherited Recessive Disorders

There are more than 1300 inherited recessive disorders (autosomal or X-linked) that affect 30 out of every 10,000 children. Some diseases have limited impact on either length or quality of life, while others are uniformly fatal in childhood.

Carrier Screening

Carrier screening is testing asymptomatic individuals to identify those who are heterozygous for serious or lethal single-gene disorders with the purpose of informing the risk of conceiving an affected child “to provide ... information to optimize pregnancy outcomes based on ... personal preferences and values.” Risk-based carrier screening is performed in individuals having an increased risk based on population carrier prevalence, and personal or family history. Conditions selected for screening can be based on ethnicities at high risk (eg, Tay-Sachs disease in Ashkenazi Jews) or may be pan-ethnic (eg, screening for cystic fibrosis carriers). Ethnicity-based screening for some conditions has been offered for decades and, in some cases, has reduced the prevalence of diseases. For example, a 90% reduction in Tay-Sachs disease followed introduction carrier screening in the 1970s in the United States and Canada. In addition, the U.S. population has become increasingly ethnically intermarried—a phenomenon the American College of Obstetricians and Gynecologists noted when offering a recommendation in 2005 for pan-ethnic cystic fibrosis carrier screening.

While methods for carrier screening of conditions individually may have been onerous in the past, contemporary molecular techniques including next-generation sequencing allow simultaneous identifying carriers of a wide range of disorders efficiently and inexpensively.

Expanded Carrier Screening

Expanded carrier screening (ECS) involves screening individuals or couples for disorders in many genes (up to 100s). The disorders included may also span a range of disease severity or phenotype. Arguments for ECS include potential issues in assessing ethnicity, ability to identify more potential conditions, efficiency, and cost. Uncertain are the possible downsides of screening individuals at low risk, including a potential for incorrect variant ascertainment and the
consequences of screening for rare single-gene disorders in which the likely phenotype may be uncertain (eg, due to variable expressivity and uncertain penetrance). The list of conditions included in ECS panels is not standardized. Although ECS panels would include conditions assessed in risk-based screening, ECS panels include many conditions not routinely evaluated and for which there are no existing professional guidelines.

This medical policy applies only if there is no separate medical policy that outlines specific criteria for carrier screening. If a separate evidence review exists, then criteria for medical necessity in that evidence review supersede the guidelines herein.

Specific Patient Populations

Carrier screening may be performed for conditions that are found in the general population (pan-ethnic), for diseases that are more common in particular populations, or based on family history.

Pan-ethnic (general population) screening for carrier status is done for single-gene disorders that are common in the population, such as cystic fibrosis.

Carrier screening for specific genetic conditions may be done in members of an ethnic group with a high risk of a specific genetic disorder. For example, certain autosomal recessive conditions are more prevalent in individuals of Eastern European Jewish (Ashkenazi) descent. Most individuals of Jewish ancestry in North America are descended from Ashkenazi Jewish communities and are therefore at increased risk of being carriers of one of these conditions. Many of these disorders are lethal in childhood or associated with significant morbidity.

FMR1 Mutations/Fragile-X Syndrome

Fragile X syndrome (FXS) is the most common inherited form of mental disability and known genetic cause of autism. The diagnosis is made with a genetic test that determines the number of CGG repeats in the fragile X gene, FMR1. FMR1 variant testing has been investigated in a variety of clinical settings, including in the evaluation of individuals with a personal or family history of intellectual disability, developmental delay, or autism spectrum disorder and in reproductive decision making in individuals with known FMR1 variants or positive cytogenetic fragile X testing. Fragile-X syndrome (FXS) is the most common cause of heritable intellectual
disability, characterized by moderate intellectual disability in males and mild intellectual
disability in females. FXS affects approximately 1 in 4000 males and 1 in 8000 females. In
addition to intellectual impairment, patients present with typical facial features, such as an
elongated face with prominent forehead, protruding jaw, and large ears. Connective tissue
anomalies include hyperextensible finger and thumb joints, hand calluses, velvet-like skin, flat
feet, and mitral valve prolapse. The characteristic appearance of adult males includes
macroorchidism. Patients may show behavioral problems including autism spectrum disorders,
sleeping problems, social anxiety, poor eye contact, mood disorders, and hand-flapping or
biting. Another prominent feature of the disorder is neuronal hyperexcitability, manifested by
hyperactivity, increased sensitivity to sensory stimuli, and a high incidence of epileptic seizures.

Fragile X syndrome (FXS) is associated with the expansion of the CGG trinucleotide repeat in the
fragile X mental retardation 1 (FMR1) gene on the X chromosome. FXS is associated with the
expansion of the FMR1 gene CGG triplet repeat above 200 units in the 5' untranslated region of
FMR1, leading to hypermethylation of the promoter region followed by transcriptional
inactivation of the gene. FXS is caused by a loss of the fragile X mental retardation protein,
which is believed to play a key role in early brain development and brain function.

Premutation alleles (55-200 CGG repeats) in females are unstable and may expand to full
mutations in offspring. Premutations of fewer than 59 repeats have not been reported to expand
to a full mutation in a single generation. Premutation alleles in males may expand or contract by
several repeats with the transmission; however, expansion to full mutations has not been
reported.

Premutation allele prevalence in whites is approximately 1 in 1000 males and 1 in 350 females. Full mutations are typically maternally transmitted. The mother of a child with an FMR1 variant is almost always a carrier of a premutation or full mutation. Women with a premutation carry a 50% risk of transmitting an abnormal gene, which contains either a premutation copy number (55-200) or a full mutation (>200) in each pregnancy.

Men who are premutation carriers are referred to as transmitting males. All of their daughters will inherit a premutation, but their sons will not inherit the premutation. Males with a full mutation usually have intellectual disability and decreased fertility.

The purpose of FMR1 testing in patients who have a personal or family history of FXS is to
inform reproductive decision making. DNA testing would accurately identify premutation
carriers and distinguish premutation from full mutation carrier women.
Table 3. Classifications of CGG Repeat Length

<table>
<thead>
<tr>
<th>Mutation Classification</th>
<th>CGG Repeat Length</th>
<th>Methylation Status</th>
<th>Variant Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full mutation</td>
<td>&gt;200 to 230</td>
<td>Methylated</td>
<td>Pathogenic variant</td>
</tr>
<tr>
<td>Premutation</td>
<td>55 to 200</td>
<td>Unmethylated</td>
<td>Pathogenic variant</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45 to 54</td>
<td>Unmethylated</td>
<td>Uncertain variant</td>
</tr>
<tr>
<td>Normal</td>
<td>5 to 44</td>
<td>Unmethylated</td>
<td>Benign variant</td>
</tr>
</tbody>
</table>

**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. In contrast, for individuals of northern European ancestry, the carrier rate is less than 1 in 1,000.

**Physiology**

Hemoglobin, which is the major oxygen carrying protein molecule of red blood cells, consists of 2 alpha (α)-globin chains and 2 beta (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 (red blood cells) 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 four genes that code for α-globin (2 copies each of HBA1 and
HBA2, located on chromosome 16), with the wild genotype (normal) being αα/αα. 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 four different syndromes, which are classified as follows:

- **Silent carrier (α-thalassemia minima):** This arises from one of four abnormal alpha genes (αα/α-), 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 (α-thalassemia minor):** This is also called α-thalassemia trait and arises from the loss of 2 α-globin genes, resulting in one of two genotypes (αα/--, or α-/-α-). A mild anemia is present, and red blood cells are hypochromic and microcytic. Clinical symptoms are usually absent and in most cases, the hemoglobin electrophoresis is normal.

- **Hemoglobin H (HbH) disease (α-thalassemia intermedia):** This syndrome results from three abnormal α-globin genes (α-/-), resulting in a 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.\(^{37}\)

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.\(^{35}\) 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.\(^{38}\)

- **Hemoglobin Bart syndrome (α-thalassemia major):** This syndrome 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.35 (See Table 4 for probability of Hemoglobin Bart Syndrome.)

**FMR1 Mutation/Fragile-X Syndrome**

Evidence on the clinical benefit of testing for Fragile-X syndrome is largely anecdotal. Clinical utility of genetic testing can be considered in the following clinical situations: (1) individuals with a clinical diagnosis of intellectual disability, developmental delay, or autism, especially if they have any physical or behavioral characteristics of Fragile-X syndrome, a family history of Fragile X syndrome, or male or female relatives with undiagnosed intellectual disability, and (2) individuals seeking reproductive counseling.

Clinical utility for these patients depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes. No studies were identified that described how a molecular diagnosis of Fragile-X syndrome changed patient management. Therefore there is no direct evidence for clinical utility of genetic testing in these patients.

Because there is no specific treatment for Fragile-X syndrome, making a definitive diagnosis will not lead to treatment that alters the natural history of the disorder. Hersh et al. (2011) reported on families with an affected male and whether an early diagnosis would have influenced their reproductive decision making.42 After a diagnosis in the affected male was made, 73% of families reported that the diagnosis of FXS affected their decision to have another child, and 43% of the families surveyed had had a second child with a full mutation. Testing the repeat region of the FMR1 gene in the context of reproductive decision making may include testing individuals with either a family history of FXS or a family history of undiagnosed intellectual disability, fetuses of known carrier mothers, or affected individuals or their relatives who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. (Cytogenetic testing was used before identification of the FMR1 gene and is significantly less accurate than the current DNA test. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women.)
Alpha-Thalassemia Preconception (Carrier) Testing

The major benefit of carrier testing is to define the likelihood of α-thalassemia major. Avoiding a pregnancy with α-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 α-thalassemia major.

Biochemical testing is recommended for all patients as the first test to identify carriers who are from an ethnic group with a high incidence of α-thalassemia. Biochemical screening consists of a CBC with peripheral smear analysis. If there are any abnormalities noted, such as anemia, microcytosis, or hypochromia, hemoglobin electrophoresis is then performed to identify the specific types of Hb present and between HbH disease. As noted, the hemoglobin electrophoresis may be normal in the asymptomatic carrier and α-thalassemia trait states, but the states may be suspected based on CBC and peripheral smear analysis.

Unlike for a clinical diagnosis, for carrier testing it is important to distinguish between α-thalassemia carrier (one abnormal gene) and α-thalassemia trait (two abnormal genes). It is also important to distinguish between the two variants of α-thalassemia trait (that is, the aa/-- [cis variant] and the a-/a- [trans variant]). This is because it is only when both parents have the aa/-- cis variant is there a risk for a fetus to have α-thalassemia major. When both parents are α-thalassemia carriers (aa/--), there is a 1 in 4 likelihood that an offspring will have α-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 HbH disease, it cannot provide a precise determination of the number or pattern of abnormal alpha genes. As a result, biochemical screening alone cannot accurately predict the probability of having a hemoglobin Bart fetus. In contrast, genetic testing can delineate the number of abnormal genes with certainty. In addition, genetic testing can determine whether an α-thalassemia trait exists as the cis (aa/-- variant or the trans (a-/a-) variant. Using this information from genetic testing, the probability of hemoglobin Bart syndrome can be determined according to the table below.
Table 4. Probability of Hemoglobin Bart Syndrome

<table>
<thead>
<tr>
<th>Clinical Diagnosis in Parents</th>
<th>Genotype (Parent 1)</th>
<th>Genotype (Parent 2)</th>
<th>Probability of Hg 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, 1 parent trait</td>
<td>aa/a-</td>
<td>a-/a-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>aa/a-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both parents trait</td>
<td>aa/-</td>
<td>aa/-</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>a/-a</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>a-/a-</td>
<td>aa/-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>a-/a-</td>
<td>a/-a</td>
<td>0</td>
</tr>
<tr>
<td>One parent HbH, 1 parent silent carrier</td>
<td>a/-&lt;sup&gt;-&lt;/sup&gt;</td>
<td>aa/a-</td>
<td>0</td>
</tr>
<tr>
<td>One parent HbH, 1 parent trait</td>
<td>a/-&lt;sup&gt;-&lt;/sup&gt;</td>
<td>aa/-</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>a/-a</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Both parents HbH</td>
<td>a-/a</td>
<td>a/-a</td>
<td>25</td>
</tr>
</tbody>
</table>

HbH: hemoglobin H

Parents can also determine the likelihood of HbH disease in an offspring through genetic testing. However, because this is in most cases a mild condition, it is less likely to be considered information that is actionable in terms of altering reproductive decision making.\textsuperscript{39}

Preconception (carrier) testing is likely to have clinical usefulness by providing incremental diagnostic information over biochemical testing. Genetic testing can identify the pattern of abnormal alpha genes and estimate more precisely the risk of hydrops fetalis.

**Summary of Evidence**

The evidence for carrier testing in individuals who are asymptomatic but at risk for having an offspring with a genetic disease includes mutation prevalence studies, general principles of carrier testing, and accepted practice guidelines from major medical societies. The evidence provides a framework for evaluating these tests because direct evidence on outcomes with carrier testing is lacking. Relevant outcomes are test accuracy, test validity and changes in
reproductive decision making. Reported analytic validity (technical accuracy) of targeted carrier screening tests is high. Changes in management involve family planning decisions. Results of genetic testing can be used to assist individuals with reproductive decisions such as avoidance of pregnancy, preimplantation genetic testing, adoption, etc. Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome. Therefore testing in this setting is considered medically necessary.

The evidence for preconception (carrier) genetic testing for alpha-thalassemia includes case reports and case series that correlate pathogenic mutations 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 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, 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 mutations is present in α-thalassemia trait. They therefore cannot completely determine the risk of a pregnancy with hemoglobin Bart 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, the evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

The evidence for FMR1 mutation testing (including Fragile X) includes studies evaluating the clinical validity of FMR1 variant testing. Relevant outcomes are test accuracy, test validity, and resource utilization. The evidence demonstrates that FMR1 variant testing can establish a definitive diagnosis of FXS and fragile X-related syndromes when the test is positive for a pathogenic variant. Following a definitive diagnosis, treatment of comorbid conditions may be improved. At a minimum, providing a diagnosis eliminates the need for further diagnostic workup. A chain of evidence supports improved outcomes following FMR1 variant testing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a personal or family history of FXS who are seeking reproductive counseling, the evidence includes studies evaluating the clinical validity of FMR1 variant testing and the effect on reproductive decision making. Testing the repeat region of the FMR1 gene in the context of reproductive decision making may include individuals with either a family history of FXS or a family history of undiagnosed intellectual disability, fetuses of known carrier
mothers, or affected individuals or their relatives who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**

A currently unpublished trial that might influence this review is listed in the Table 5 below.

**Table 5: Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01902901</td>
<td>Clinical Implementation of Carrier Status Using Next Generation Sequencing</td>
<td>400</td>
<td>May 2018</td>
</tr>
</tbody>
</table>

NCT: National Clinical Trial

**Practice Guidelines and Position Statements**

*Risk-Based Condition-Specific Screening Recommendations*

The American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics and Genomics (ACMG) have issued numerous guidelines on conditions discussed herein. Table 6 provides the recommendations by indication for risk-based screening.

**Table 6. ACOG and ACMG Recommendations for Risk-Based Screening**

<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendation</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Society</td>
<td>Recommendation</td>
<td>Year</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>ACOG</td>
<td>“Cystic fibrosis carrier screening should be offered to all women considering pregnancy or are pregnant.”</td>
<td>2017</td>
</tr>
<tr>
<td>ACMG</td>
<td>Current ACMG guidelines use a 23-variant panel and were developed after assessing the initial experiences on implementation of cystic fibrosis screening into clinical practice. Using the 23-variant panel, the detection rate is 94% in the Ashkenazi Jewish population and 88% in the non-Hispanic white general population.</td>
<td>2013</td>
</tr>
</tbody>
</table>
| Spinal muscular atrophy<sup>b</sup>   | **ACOG**  
“Screening for spinal muscular atrophy should be offered to all women considering pregnancy or are pregnant. In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, SMN1 deletion testing should be recommended for the low-risk partner.” | 2017 |
|                                                                                               | **ACMG**  
Because spinal muscular atrophy is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity. | 2013 |
| Tay-Sachs disease                                                                                                     | **ACOG**  
“Screening for Tay-Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French-Canadian, or Cajun descent. Those with a family history consistent with Tay-Sachs disease should also be screened.” | 2017 |
| Hemoglobinopathies (sickle cell disease, α- and β-thalassemia)               | **ACOG**  
“A complete blood count with red blood cell indices should be performed in all women who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of a hemoglobinopathy. Ideally, this testing also should be offered to women before pregnancy. A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent). If red blood cell indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume, hemoglobin electrophoresis also should be performed.” | 2017 |
| Fragile-X syndrome                                                                                      | **ACOG**  
“Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant. If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an FMR1 premutation.” | 2017 |

ACMG: American College of Medical Genetics and Genomics; ACOG: American College of Obstetricians and Gynecologists.
Carrier rates: Ashkenazi Jews 1/24, non-Hispanic white 1/25, Hispanic white 1/58, African American 1/61, Asian American 1/94.

General population carrier rate: 1/40 to 1/60.

Ashkenazi Jewish Populations

Individuals of Ashkenazi Jewish descent have high carrier rates for multiple conditions—cumulatively between 1 in 4 and 1 in 5 when all disorders are considered. Recommendations for carrier screening for Ashkenazi Jewish individuals by ACOG and ACMG are summarized in Table 7. According to ACMG, if only 1 member of the couple is Jewish, ideally, that individual should be tested first. If the Jewish partner has a positive carrier test result, the other partner (regardless of ethnic background) should be screened for that particular disorder. One Jewish grandparent is sufficient to offer testing.

Table 7. ACMG (2008, 2013) and ACOG (2017) Carrier Screening Recommendations for Individuals of Ashkenazi Jewish Descent

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sachs disease</td>
<td>1/3000</td>
<td>1/30</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>1/6400</td>
<td>1/40</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1/2500-3000</td>
<td>1/29</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Familial dysautonomia</td>
<td>1/3600</td>
<td>1/32</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Fanconi anemia (group C)</td>
<td>1/32,000</td>
<td>1/89</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Niemann-Pick disease type A</td>
<td>1/32,000</td>
<td>1/90</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>1/40,000</td>
<td>1/100</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Mucolipidosis IV</td>
<td>1/62,500</td>
<td>1/127</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>1/900</td>
<td>1/15</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Familial hyperinsulinism</td>
<td></td>
<td>1/52</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Glycogen storage disease type I</td>
<td></td>
<td>1/71</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td></td>
<td>1/92</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>1/81</td>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Usher syndrome</td>
<td>≤ 1/40</td>
<td></td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; ACOG: American College of Obstetricians and Gynecologists; C: should be considered; R: recommended.

Expanded Carrier Screening Recommendations

**American College of Obstetricians and Gynecologists**

In 2017, ACOG made the following recommendations on expanded carrier screening (ECS)\(^30\):

- Ethnic-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Each obstetrician-gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. After counseling, a patient may decline any or all carrier screening.

- Expanded carrier screening does not replace previous risk-based screening recommendations.

Based on “consensus,” characteristics of included disorders should meet the following criteria:

- Carrier frequency ≥1/100
- “Well-defined phenotype”
- “Detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life”
- Not be primarily associated with a disease of adult onset.

ACOG also noted that ECS panels may not offer the most sensitive detection method for some conditions such as Tay-Sachs disease (ie, they will miss carrier state in up to 10% of low-risk populations) or hemoglobinopathies.

ACOG also provided a detailed example of an ECS panel that includes testing for 22 conditions: α-thalassemia, β-thalassemia, Bloom syndrome, Canavan disease, cystic fibrosis, familial...
dysautonomia, familial hyperinsulinism, Fanconi anemia C, fragile X syndrome, galactosemia, Gaucher disease, glycogen storage disease type 1A, Joubert syndrome, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease types 1A and 1B, mucolipidosis IV, Niemann-Pick disease type A, phenylketonuria, sickle cell anemia, Smith-Lemli-Opitz syndrome, spinal muscular atrophy, and Tay-Sachs disease.

In 2015, a joint statement on ECS was issued by ACOG, ACMG, the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine. The statement was not intended to replace current screening guidelines but to demonstrate an approach for health care providers and laboratories seeking to or currently offering ECS panels. Some points considered included the following.

- “Expanded carrier screening panels include most of the conditions recommended in current guidelines. However, molecular methods used in expanded carrier screening are not as accurate as methods recommended in current guidelines for the following conditions:
  a. Screening for hemoglobinopathies requires use of mean corpuscular volume and hemoglobin electrophoresis.
  b. Tay-Sachs disease carrier testing has a low detection rate in non-Ashkenazi populations using molecular testing for the three common Ashkenazi mutations. Currently, hexosaminidase A enzyme analysis on blood is the best method to identify carriers in all ethnicities.”

- “Patients should be aware that newborn screening is mandated by all states and can identify some genetic conditions in the newborn. However, newborn screening may include a different panel of conditions than ECS. Newborn screening does not usually detect children who are carriers for the conditions being screened so will not necessarily identify carrier parents at increased risk.”

- “Expanded carrier screening can be performed by genotyping or by DNA sequencing. Genotyping searches for known pathogenic and likely pathogenic variants. Sequencing analyzes the entire coding region of the gene and identifies alterations from the normal sequence. Although genotyping includes only selected variants, sequencing has the potential to identify not only benign, but also likely benign variants. Sequencing also can identify variants of uncertain significance....
• ECS panels should only include “genes and variants” with “a well-understood relationship with a phenotype…. When the carrier frequency and detection rate are both known, residual risk estimation should be provided in laboratory reports.”

• Conditions with unclear value on preconception and prenatal screening panels include α1-antitrypsin, methylene tetrahydrofolate reductase, and hereditary hemochromatosis

The statement also included a set of recommendations for screened conditions:

• “The condition being screened for should be a health problem that encompasses one or more of the following:
  - Cognitive disability
  - Need for surgical or medical intervention
  - Effect on quality of life
  - Conditions for which a prenatal diagnosis may result in:
    - Prenatal intervention to improve perinatal outcome and immediate care of the neonate
    - Delivery management to optimize newborn and infant outcomes such as immediate, specialized neonatal care. Prenatal education of parents regarding special needs care after birth; this often may be accomplished most effectively before birth.”
    - Prenatal education of parents regarding special needs care after birth; this often may be accomplished most effectively before birth.”

In 2017, the American College of Obstetricians and Gynecologists recommended that screening for FXS be offered to women with a family history suggestive of FXS and to women with a medical history suggestive of being a fragile X carrier (ie, ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40). The College recommended prenatal diagnostic testing for FXS to known carriers of the fragile X premutation or full mutation.
American College of Medical Genetics and Genomics

In 2013, ACMG issued a position statement on prenatal/preconception expanded carrier testing. For a particular disorder to be included in carrier screening, the following criteria should be met:

- "Disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction.
  
  o The inclusion of disorders characterized by variable expressivity or incomplete penetrance and those known to be associated with a mild phenotype should be optional and made transparent when using these technologies for screening. This recommendation is guided by the ethical principle of nonmaleficence.

- When adult-onset disorders (disorders that could affect offspring of the individual undergoing carrier screening once offspring reach adult life) are included in screening panels, patients must provide consent to screening for these conditions, especially when there may be implications for the health of the individual being screened or for other family members.
  
  o This recommendation follows the ethical principles of autonomy and nonmaleficence.

- For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed.
  
  o Laboratories should specify in their marketing literature and test results how residual risk was calculated using pan-ethnic population data or a specific race/ethnic group.

  o The calculation of residual risk requires knowledge of 2 factors: one is the carrier frequency within a population, the other is the proportion of disease-causing alleles detected using the specific testing platform. Laboratories using multiplex platforms often have limited knowledge of one or both factors. Laboratories offering expanded carrier screening should keep data prospectively and regularly report findings that allow computation of residual risk estimates for all disorders being offered. When data are inadequate, patient materials must stress that negative results should not be over interpreted.
• There must be validated clinical association between the mutation(s) detected and the severity of the disorder.
  
  o Patient and provider materials must include specific citations that support inclusion of the mutations for which screening is being performed.

• ECS tests must comply with the American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories, including quality control and proficiency testing.
  
  o Quality control should include the entire test process, including preanalytical, analytical, and postanalytical phases. Test performance characteristics should be available to patients and providers accessing testing.
  
  o A highly multiplexed approach will require a more generic consent process than is typically used for single-disease screening because it may be impractical for a clinician to discuss each disease included in a multidisease carrier screening panel. An appropriately tailored informational pamphlet or Web site, containing a brief description of each disorder included in a test panel, should be available to patients undergoing or considering an expanded prenatal/preconception carrier screening panel. Genetic counseling before testing should be available to those who desire this, and posttest genetic counseling for those with positive screening results is recommended.”

The American College of Medical Genetics and Genomics (ACMG) made the following recommendations in 2005 on diagnostic and carrier testing for fragile X syndrome (FXS). The purpose of these recommendations was to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the FMR1 gene.

• Individuals of either sex with mental retardation, developmental delay, or autism, especially if they have (a) any physical or behavioral characteristics of fragile X syndrome, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation.

• Individuals seeking reproductive counseling who have (a) a family history of fragile X syndrome, or (b) a family history of undiagnosed intellectual disability.

• Fetuses of known carrier mothers.

• Affected individuals or their relatives in the context of a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among
themselves or their relatives. The cytogenetic test was used before the identification of the FMR1 gene and is significantly less accurate than the current DNA test. DNA testing on such individuals is warranted to accurately identify premutation carriers and to distinguish premutation from full mutation carrier women.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force makes recommendations for carrier testing for BRCA-associated genetic diseases and for hereditary hemochromatosis, topics that are not included herein but in the medical policies for each condition (see Related Policies).

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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

There are a number of commercially available genetic tests for carrier screening. These range from testing for individual diseases, to small panels designed to address testing based on ethnicity as recommended by practice guidelines (American College of Obstetricians and Gynecologists [ACOG], American College of Medical Genetics and Genomics [ACMG]), to large expanded panels that test for numerous diseases beyond those recommended in practice guidelines. The following is a list of some of the available panels, but it is not comprehensive:

- **Counsyl™ (Counsyl):** Tests for more than 100 diseases, which, according to the manufacturer’s website, lead to shortened lifespan, have limited treatment or can lead to intellectual disability. Diseases tested for include those recommended by ACOG, ACMG, as
well as an Ashkenazi Jewish panel, Fragile-X syndrome, a 100-mutation CF panel, sickle cell disease, and metabolic disorders.

- **GoodStart Select™ (GoodStart Genetics):** “Customizes” the testing panel for each patient based on ethnicity, family history, and provider testing preferences. The test menu includes several ethnic panels, and includes testing for hemoglobinopathies, Fragile-X syndrome, CF, metabolic disorders, and others.

- **Inherigen™ (GenPath):** A pan-ethnic test for over 160 inherited disorders, typically those with childhood onset and severe symptoms. It includes testing for some immunodeficiencies as well as for several metabolic diseases such as Tay-Sachs disease, glycogen storage diseases, and fatty acid oxidation disorders. InheriGen Plus includes all InheriGen diseases plus CF, SMA, and Fragile-X syndrome.

- **Inheritest™ (LabCorp):** A pan-ethnic test for more than 90 autosomal recessive inherited diseases. The Inheritest Select Carrier Screen is a test that evaluates diseases for patients of Ashkenazi Jewish descent.

- **Natera One™ Disease Panel (Natera):** Tests for 13 diseases, which include ACMG-recommended tests for carrier screening, plus Fragile-X syndrome, sickle cell anemia, hemoglobin C trait, and SMA.

Natera Horizon has 5 different panels that screen for as few as 4 and up to 274 autosomal and X-linked genetic conditions. The panels are pan-ethnic, ancestry-based or expanded.

Two CLIA-certified laboratories, Progenity™ (Ann Arbor, Michigan; formerly aMDx Laboratory Sciences and Ascendant MDx) and Sequenom® Laboratories (San Diego, CA), offer both single disease carrier testing (cystic fibrosis [CFnxt cystic fibrosis and HerediT™ Cystic Fibrosis Carrier Screen, respectively], fragile X syndrome [Fragile X syndrome and HerediT™ Cystic Fibrosis Carrier Screen, respectively], SMA [SMAnxt spinal muscular atrophy and HerediT™ Spinal Muscular Atrophy Carrier Screen, respectively] and disease panels for Ashkenazi Jewish patients (AJPnxt Basic [9 diseases] or AJPnxt Expanded [19 diseases] and HerediT™ Ashkenazi Jewish Panel Carrier Screen [17 diseases], respectively). Progenity™ also offers nxtPanel for simultaneous CF, SMA, and fragile X syndrome testing.


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/01/16</td>
<td>Interim update, approved April 12, 2016. Genetic Testing for Alpha-Thalassemia incorporated into this policy for ease of use. New policy statement added: Fragile-X Syndrome testing may be considered medically necessary when criteria are met.</td>
</tr>
<tr>
<td>07/01/16</td>
<td>Policy moved to new format. No change in content or coverage.</td>
</tr>
<tr>
<td>08/01/16</td>
<td>Interim Update, approved July 12, 2016. Policy statement on genetic testing for FMR1 mutations changed from investigational to not medically necessary. Policy statements of not medically necessary added to testing for Ashkenazi Jewish Founder and Other Inherited Disorders when criteria are not met.</td>
</tr>
<tr>
<td>07/17/18</td>
<td>Minor edit for clarification; Added CPT codes 81400, 81401 to Spinal Muscular Atrophy for clarity regarding coding.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and
local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentinquuries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon yon lan oswa konvènt kouvèti asirans lan atrave Premera Blue Cross. Kapab genyen dat ki enpotan nan av si sila a. Ou ka gen pou kan kék aksyon avan sèten dat limit pou ka konbo kouvèti asirans sante w la oswa pou yo ka ede ede av ak depans yo. Se dwa w pou reserwa enfòmasyon sa a ak assisted nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):

Iloko (Ilocano):
Daytoy a Pakdaad ket naglaon iti Napateg nga Impomars. Daytoy a pakdaad mabalini nga adda ket naglaon iti napateg nga impomars maipeange tito aplikasyon ni yowo kay coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a penta iti daytoy a pakdaad. Mabalini nga adda rumbeng nga aramideni nga adda sakyab dagiti partikular a naituding nga adda tapo napo mamatgalaydiyo tito coverage ti salan-atyo yowo tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impomars ken tulong iti bukodo a pagasao nga awan ti bayadanyo. Tumawig iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要日期，您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).
Premera Blue Cross: This Notice contains important information. This Notice may be given to you by Premera Blue Cross through Premera Blue Cross. This does not mean Premera Blue Cross is giving you this Notice because it has received a request to do so. Furthermore, this Notice is given to you so that you may be aware of important information and be able to take action if necessary.

Español (Spanish): Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso importante. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Русский (Russian): Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

العربية (Arabic): يحتوي هذا الرسالة على معلومات هامة. لا يعني أن نحن نرسل هذه الرسالة لأننا رأينا الحاجة إلى ذلك. هذا الرسالة فقط لكي تكون لديك معلومات هامة وتمكنك من أن تتخذ تدابيرًا إذا كانت ضرورية.


Українська (Ukrainian): Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує можливість того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).