MEDICAL POLICY – 12.04.518
Preconception Screening for Carrier Status of Genetic Diseases


Effective Date: July 1, 2017
Last Revised: June 22, 2017
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

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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 Screening Panels</td>
<td>Expanded carrier screening panels which test for mutations on many different genes are considered not medically necessary. 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>
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<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></td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>Covered for all individuals with a panel that tests the most common genes (CPT 81220)</td>
</tr>
<tr>
<td></td>
<td><strong>Note:</strong> Carrier testing for cystic fibrosis using CPT 81223 “CFTR (e.g. cystic fibrosis) gene analysis; full gene sequence” is considered not medically necessary for carrier testing.</td>
</tr>
</tbody>
</table>
### Genetic Disease | Medical Necessity
---|---
**Spinal Muscular Atrophy** | Covered for all individuals

### 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>Genetic Disease</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ashkenazi Jewish founder mutations:</strong></td>
<td>May be considered medically necessary when the individual meets one of the following criteria:</td>
</tr>
<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>Genetic 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><strong>FMR1 mutations (including Fragile-X syndrome)</strong></th>
<th>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></td>
</tr>
<tr>
<td>Parent with a family history of fragile X syndrome or a family history of undiagnosed intellectual disability</td>
<td></td>
</tr>
<tr>
<td>Mothers who are known carriers to determine whether the fetus inherited the normal or mutant FMR1 gene</td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
</tbody>
</table>

**FMR1 mutations (including Fragile-X syndrome) is considered not medically necessary for all other uses.**

<table>
<thead>
<tr>
<th><strong>Alpha-thalassemia preconception (carrier)</strong></th>
<th>May be considered medically necessary when all of the following criteria are met:</th>
</tr>
</thead>
</table>

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### Genetic Disease

<table>
<thead>
<tr>
<th>Genetic Disease</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| testing                          | • 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

<table>
<thead>
<tr>
<th>Genetic Disease</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Carrier testing of specific disorder | May be considered medically necessary when any of the following are present:  
• One or both parents have a first- or second-degree relative who has the disorder:  
  o 1st-degree relatives are parents, siblings, and children.  
  o 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.  
• One parent is or both parents are a known carrier of the disorder.  

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 less accurate than genetic testing  
• The genetic test has adequate sensitivity and specificity to guide clinical decision making  
  o The American College of Medical Genetics and Genomics (ACMG) recommends testing for specific mutations, which |
Genetic Disease | Medical Necessity
--- | ---
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>
<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., 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)</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), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

### Related Information

**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 (e.g., 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.

**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**

**Background**

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 is performed to identify couples at risk of having offspring with a genetic disease. Carriers are usually not at risk of developing the disease, but have a risk of passing a pathogenic gene mutation to their offspring. Carrier testing may be performed before conception or during a pregnancy.

**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 is associated with the expansion of the CGG trinucleotide repeat in the fragile-X mental retardation 1 (FMR1) gene on the X chromosome.

Fragile-X syndrome (FXS) is the most common cause of heritable intellectual disability. Affected individuals show 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.

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.

**Alpha-Thalassemia**

Alpha-thalassemia is a common genetic disorder, affecting approximately 5% of the world’s population. The frequency of mutations 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.

Hemoglobin, 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 aa/aa. Genetic mutations may occur in any or all of these 4 α-globin genes. The number of genetic mutations determines the phenotype and severity of the α-thalassemia syndromes. The different syndromes are classified as follows:

- **Silent carrier (α-thalassemia minima):** This arises from one of four abnormal alpha genes (aa/a-), and is a silent carrier state. A small amount of abnormal hemoglobin can be detected in the peripheral blood, and there may be mild hypochromia and microcytosis present, but there is no anemia or other clinical manifestations.

- **Thalassemia trait (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 (aa/-/-, or a-/a-). A mild anemia is present, and red blood cells are hypochromic and microcytic. Clinical symptoms are usually absent and in most cases, the Hg electrophoresis is normal.

- **Hemoglobin H disease (α-thalassemia intermedia):** This syndrome results from three abnormal α-globin genes (a-/--), resulting in a moderate to severe anemia. In HgH 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.

A minority of individuals may develop clinical symptoms of chronic hemolytic anemia. These include neonatal jaundice, hepatosplenomegaly, hyperbilirubinemia, leg ulcers, and premature development of biliary tract disease. Splenomegaly can lead to the need for splenectomy, and transfusion support may be required by the third to fourth decade of life. It has been estimated that approximately 25% of patients with HgH disease will require transfusion support during their lifetime. 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 HgH disease.

There is an association between genotype and phenotype among patients with HgH disease. Individuals with a nondeletion mutation typically have an earlier presentation, more severe anemia, jaundice, and bone changes, and more frequently require transfusions.

- **Hemoglobin Bart syndrome (α-thalassemia major):** This syndrome results from mutations in all 4 α-globin genes (---/---), resulting in absent 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 of pregnancy for a woman carrying a fetus with hydrops fetalis. These include hypertension, preeclampsia, antepartum hemorrhage, renal failure, premature labor, and abruptio placenta. (See Table 1 for probability of Hoemoglobin 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. There are several potential ways in which adjunctive management might be changed after confirmation of the diagnosis by genetic testing. The American Academy of Pediatrics (AAP)\textsuperscript{5} and the American Academy of Neurology (AAN) recommend cytogenetic evaluation in individuals with developmental delay to look for certain chromosomal abnormalities that may be causally related to their condition. AAN guidelines note that only in occasional cases will an etiologic diagnosis lead to specific therapy that improves outcomes but suggest more immediate and general clinical benefits of achieving a specific genetic diagnosis from the clinical viewpoint, as follows:

- Limit additional diagnostic testing;
- Anticipate and manage associated medical and behavioral comorbidities;
- Improve understanding of treatment and prognosis; and
- Allow counseling regarding risk of recurrence in future offspring and help with reproductive planning.

AAP and AAN guidelines also emphasize the importance of early diagnosis and intervention in an attempt to ameliorate or improve behavioral and cognitive outcomes over time. Guidelines from AAP recommend against routine fragile X testing for children with isolated attention-deficit/hyperactivity disorder.

**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, Hg electrophoresis is then performed to identify the specific types
of Hg present and between HgH 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 that there is 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 HgH 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 1. 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></td>
<td>aa/a--</td>
<td>0</td>
</tr>
<tr>
<td>Both parents trait</td>
<td>aa/--</td>
<td>aa/--</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a-/a-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>a-/a-</td>
<td>aa/--</td>
<td>0</td>
</tr>
<tr>
<td>Clinical Diagnosis in Parents</td>
<td>Genotype (Parent 1)</td>
<td>Genotype (Parent 2)</td>
<td>Probability of Hg Bart Syndrome, %</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td></td>
<td>a-/a-</td>
<td>a-/a-</td>
<td>0</td>
</tr>
<tr>
<td>One parent HgH, 1 parent silent carrier</td>
<td>a-/--</td>
<td>aa/a-</td>
<td>0</td>
</tr>
<tr>
<td>One parent HgH, 1 parent trait</td>
<td>a-/--</td>
<td>aa/--</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>a-/a-</td>
<td>a-/a-</td>
<td>25</td>
</tr>
<tr>
<td>Both parents HgH</td>
<td>a-/--</td>
<td>a-/--</td>
<td>25</td>
</tr>
</tbody>
</table>

Hg: hemoglobin

Parents can also determine the likelihood of HgH 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.

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

**Expanded Carrier Screening Panels**

**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.
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 qualitatively 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 analytic and clinical validity of FMR1 mutation testing and a chain of indirect evidence for demonstration of clinical outcome improvements. Relevant outcomes are test accuracy, test validity, resource utilization, and changes in reproductive decision making. Analytic sensitivity and specificity for diagnosing these disorders has been demonstrated to be sufficiently high. The evidence demonstrates that FMR1 mutation testing can establish a definitive diagnosis of FXS when the test is positive for a pathogenic mutation. Following a definitive diagnosis, there are a variety of ways management may change. Providing a diagnosis can eliminate the need for
further clinical workup. For certain mutations, results may aid in management of psychopharmacologic interventions, assist in informed reproductive decision making, or both. Although direct evidence for improved outcomes is insufficient, there is a chain of indirect evidence that supports improvements in outcomes following FMR1 mutation testing. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic but at risk for having offspring with inherited single-gene disorders who receive expanded carrier screening, the evidence includes studies concerning analytic validity, clinical validity, and indirectly clinical utility. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. The analytic validity of ECS panels will depend on the molecular method used; 2 identified studies support the analytic validity for ECS, but variant ascertainment with NGS requires careful evaluation. Three studies have found that ECS identifies more carriers and potentially affected fetuses. However, evidence to support the clinical validity of expanding carrier screening beyond risk-based recommendations is limited and accompanied by some concerns including: interlaboratory agreement of variant pathogenicity assessment when sequencing identifies rare variants, the validity of disease severity classifications for rare disorders, and the certainty of predicted risk that the offspring will be affected by severe phenotype for all the disorders included in a panel. The evidence is insufficient to determine the effects of the technology on health outcomes. Therefore this testing is considered investigational.

**Ongoing and Unpublished Clinical Trials**

A currently unpublished trial that might influence this review is listed in the **Table 2** below.

**Table 2: Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>Ongoing</td>
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<tr>
<td>NCT01902901</td>
<td>Clinical Implementation of Carrier Status Using Next Generation Sequencing</td>
<td>400</td>
<td>May 2017</td>
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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 3 provides the recommendations by indication for risk-based screening.

Table 3. 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><strong>Cystic Fibrosis</strong>&lt;sup&gt;a&lt;/sup&gt;</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.”&lt;sup&gt;26&lt;/sup&gt;</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.&lt;sup&gt;27&lt;/sup&gt;</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Spinal muscular atrophy</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACOG</td>
<td>“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.”&lt;sup&gt;26&lt;/sup&gt;</td>
<td>2017</td>
</tr>
<tr>
<td>ACMG</td>
<td>Because spinal muscular atrophy is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity.&lt;sup&gt;28&lt;/sup&gt;</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Tay-Sachs disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACOG</td>
<td>“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 be offered carrier testing.”&lt;sup&gt;26&lt;/sup&gt;</td>
<td>2017</td>
</tr>
<tr>
<td>Society</td>
<td>Recommendation</td>
<td>Year</td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>Hemoglobinopathies (sickle cell disease, α- and β-thalassemia)</td>
<td>“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.”</td>
<td>2017</td>
</tr>
</tbody>
</table>

### Fragile-X syndrome

<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendation</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG</td>
<td>“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.”</td>
<td>2017</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; ACOG: American College of Obstetricians and Gynecologists.

a Carrier rates: Ashkenazi Jews 1/24, non-Hispanic white 1/25, Hispanic white 1/58, African American 1/61, Asian American 1/94.

b 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 4. 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 4. 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>1/52</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Glycogen storage disease type I</td>
<td>1/71</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>1/92</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>1/81</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Usher syndrome</td>
<td>≤ 1/40</td>
<td></td>
<td></td>
<td>C</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):

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 $\geq 1/100$
- “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.”

**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.

  - 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.
- 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.

  - 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.

  - 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.

  - 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.

  - 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.

    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.

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 see evidence reviews for each condition (see Related Policies).

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, 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 Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

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.

**References**


30. Grody WW. Where to draw the boundaries for prenatal carrier screening. JAMA. Aug 16 2016;316(7):717-719. PMID 27533155


### History

<table>
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<tr>
<th>Date</th>
<th>Comments</th>
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<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>
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</table>

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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Avis sila a gen Enfòmasyon Enpòtand laadjan. Avis sila a kapab genyen enfòmasyon enpòtan konsènyan aplikasyon w lan oswa konèsan koudwè kòsaës lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avis sila a. Ou ka gen pou pou pan kék aksyon avan sente dat limit pou ka kente koudwè kòsaës sante w la oswa pou yo ka ede w avèk defans yo. Se dwa w pou resewa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5537).

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Hmoob (Hmong):

Illoko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maijanggip iti aplikasyonu wayno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a peseta iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga adding sakbay dagiti partikular a na italuding nga adda aldaw tapno mapagtalainedyo ti coverage ti salun-ayno wayno tulog kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulog ti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5537).

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