Carrier Screening for Genetic Diseases

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

RELATED PROTOCOLS

Genetic Testing for Hereditary Hemochromatosis
Genetic Testing for Mitochondrial Disorders
Germline Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
Invasive Prenatal (Fetal) Diagnostic Testing
Preimplantation Genetic Testing

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<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<td>Individuals: • Who are asymptomatic but at risk for having an offspring with inherited X-linked or autosomal recessive single-gene disorder</td>
<td>Interventions of interest are: • Targeted risk-based carrier screening</td>
<td>Comparators of interest are: • No carrier screening</td>
<td>Relevant outcomes include: • Test validity • Changes in reproductive decision making</td>
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<td>Individuals: • Who are either at increased risk or population risk of having offspring with an inherited X-linked or autosomal recessive genetic disorder</td>
<td>Interventions of interest are: • Non-targeted carrier screening panel</td>
<td>Comparators of interest are: • Targeted risk-based carrier screening</td>
<td>Relevant outcomes include: • Test validity • Changes in reproductive decision making</td>
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DESCRIPTION

Carrier screening is performed to identify individuals at risk of having offspring with inherited recessive 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.

SUMMARY OF EVIDENCE
For individuals who are asymptomatic but at risk for having offspring with an inherited X-linked or autosomal recessive genetic disorder who receive targeted risk-based carrier screening, the evidence includes studies supporting clinical validity and clinical utility. Relevant outcomes are test validity and changes in reproductive decision making. Results of carrier testing can be used to inform reproductive decisions such as preimplantation genetic diagnosis, in vitro fertilization, not having a child, invasive prenatal testing, adoption, or pregnancy termination. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are either at increased risk or population risk for having offspring with an inherited X-linked or autosomal recessive genetic disorder who receive a non-targeted carrier screening panel, the evidence includes studies supporting clinical validity and clinical utility. Relevant outcomes are test validity and changes in reproductive decision making. Studies have found that non-targeted carrier screening identifies more carriers and more potentially affected fetuses. Many of the genes in carrier screening panels do not meet the American College of Obstetricians and Gynecologists consensus-driven criteria of at least 1% carrier rate for all ethnic groups. However, non-targeted testing can address the discrepancies between self-reported ethnicity and genetic ancestry in an ethnically mixed population. As panels become larger the likelihood of being identified as a carrier of a rare genetic disorder increases, leading to an at-risk couple rate of nearly 2% for having an offspring with a recessive or X-linked disorder. Many, though notably not all, of these rare genetic disorders are associated with severe or profound symptoms including shortened lifespan and intellectual or physical disability. With adequate genetic counseling, carrier screening panels can inform reproductive choices, and observational studies have shown that a majority of couples would consider intervention that depends on the severity of the condition. Therefore, non-targeted carrier screening panels for severe recessive and X-linked genetic disorders can have a significant clinical impact. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

POLICY
TARGETED RISK-BASED CARRIER SCREENING
Targeted carrier screening for X-linked and autosomal recessive genetic diseases is considered medically necessary for members who are pregnant or are considering pregnancy and are at increased risk of having offspring with an X-linked or autosomal recessive disease when one of the following criteria is met:

- One or both individuals have a first- or second-degree relative who is affected OR
- One individual is known to be a carrier OR
- One or both individuals are members of a population known to have a carrier rate that exceeds a threshold considered appropriate for testing for a particular condition.

AND all of the following criteria are met:

- The natural history of the disease is well understood and there is a reasonable likelihood that the disease is one with high morbidity or early mortality in the homozygous or compound heterozygous state (see Policy Guidelines);
• Alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing;
• The genetic test has adequate clinical validity to guide clinical decision making and residual risk is understood;
• An association of the marker with the disorder has been established;
• If targeted testing is performed by a panel, the panel meets the minimum number of recommended gene variants but does not exceed the maximum, as determined by professional clinical guidelines (see Policy Guidelines). Non-targeted panels can be used instead of targeted testing when the criteria for non-targeted carrier screening are met (see below);
• Previous carrier screening or individual targeted gene testing for the gene variant(s) of interest has not been performed (see Policy Guidelines).

All targeted screening not meeting any of the above criteria is considered not medically necessary.

First-degree relatives include a biological parent, brother, sister, or child; second-degree relatives include biologic grandparent, aunt, uncle, niece, nephew, grandchildren, and half-sibling.

NON-TARGETED CARRIER SCREENING

Non-targeted carrier screening panels for autosomal recessive and X-linked genetic disorders may be considered medically necessary as an alternative to testing of individual genes (e.g., SMN1 gene and CFTR gene) for members who are pregnant or are considering pregnancy at any risk level including high risk and average risk when all of the following criteria are met:
• The natural history of each disease is well understood and there is reasonable likelihood that the disease is one with high morbidity or early mortality in the homozygous or compound homozygous state (see Policy Guidelines);
• Alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing;
• The genetic test has adequate clinical validity to guide clinical decision-making and residual risk is understood;
• An association of the markers with the disorders has been established;
• If testing is performed by a panel, the panel meets the minimum number of recommended gene variants but does not exceed the maximum, as determined by professional clinical guidelines (see Policy Guidelines);
• Previous carrier screening has not been performed (see Policy Guidelines).

Non-targeted carrier screening panels are considered investigational in all other situations when above criteria are not met (see Policy Guidelines).

POLICY GUIDELINES

This protocol doesn’t address Fragile X syndrome – refer to Genetic Testing for FMR1 Variants (Including Fragile X Syndrome) Protocol.

Carrier screening (targeted or non-targeted) is only medically necessary once per lifetime. Exceptions may be considered if advances in technology support medical necessity for retesting.
Targeted carrier screening for autosomal recessive or X-linked conditions is also called risk-based test or ethnic-based testing. Non-targeted carrier screening panels should include the minimum number of genes but not exceed the maximum number of genes recommended by professional guidelines from the American College of Obstetricians and Gynecologists (ACOG; 2-22 conditions) or the American College of Medical Genetics and Genomics (ACMG; 113 genes).

The ACOG Committee Opinion 690 (reaffirmed in 2020) states that “Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening” and offered the following summary pertaining to expanded carrier screening: “Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth. Carrier screening panels should not include conditions primarily associated with a disease of adult onset.”

The ACOG guideline includes a list of 22 conditions deemed reasonable to include in a carrier screening panel (see Appendix 2). While there is no agreed upon definition of severity across professional societies, these 22 conditions have severity that would be deemed profound or severe per publication based on previous work by ACMG and cited by the most recent ACMG guidelines. All but one condition deemed reasonable by ACOG (alpha-thalassemia) would be classified as profound or severe based on collaborative clinical expert application of a trait-based algorithm; however, in this work it is not clear if the alpha-thalassemia genes HBA1/HBA2 were classified based on hemoglobin Bart hydrops fetalis syndrome or hemoglobin H disease. Carrier testing of autosomal recessive genes associated with severe disease with carrier frequency of greater than 1/100 is estimated to identify 82% of at-risk couples.

In 2021, the ACMG recommended that the phrase “expanded carrier screening” be replaced by “carrier screening” as expanded carrier screening is not well or precisely defined by professional organizations. Previously, 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 (e.g., ethnic-specific screening or panethnic testing for cystic fibrosis).

The updated ACMG guideline now recommends a multi-tier approach to carrier screening for autosomal recessive and X-linked conditions, incorporating recommendations from the ACOG Committee Opinion 691 (2017), to enhance communication and precision while advancing equity in carrier screening (see Table PG1). The consensus group recognized no accepted standard in defining the severity of various conditions; and, based on previous work, use the following definitions: (1) profound: shortened lifespan during infancy or childhood, intellectual disability; (2) severe: death in early adulthood, impaired mobility or a [disabling] malformation involving an internal organ; (3) moderate: neurosensory impairment, immune deficiency or cancer, mental illness, dysmorphic features; and (4) mild: not meeting one of those described.

The ACMG consensus group recommends offering Tier 3 carrier screening (≥1/200 carrier frequency + Tier 2; see Table PG1) to all pregnant patients and those planning a pregnancy. Carrier testing of autosomal recessive genes associated with severe disease with carrier frequency greater than 1/100 is estimated to identify 82% of at-risk couples, and identify 93% of at-risk couples when testing for genes with greater than 1/200 carrier frequency. The ACMG Tier 3 recommendations were based on estimates that moving from Tier 2 (≥1/100 carrier frequency) to Tier 3 (1/200 carrier frequency) provided additional identification of 4-9/10,000 at-risk couples depending on the endogamous population examined. When the population evaluated was weighted by U.S. census data, at-risk couples identified increased by 6 per 10,000 couples when moving from the Tier 2 (≥1/100) carrier frequen-
cy to that of Tier 3 (≥1/200). Assuming ~4 million births per year, this translates to an annual increase of identifying 2,400 additional U.S. couples.

The ACMG consensus group specified gene recommendations which include testing for 97 autosomal recessive genes and 16 X-linked genes, all of which associate with disorders of moderate, severe, or profound severity and are of 1/200 or greater carrier frequency. Non-targeted carrier screening panels that test for genes beyond this provide diminishingly small results, and pleiotropy, locus heterogeneity, variant interpretation, and poor genotype-phenotype correlation may disproportionately impact the ability to provide accurate prognostic information.3

Additionally, the recommendations include that male partners of pregnant women and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions when carrier screening is performed simultaneously with their female partner. Tier 4 screening may be offered when a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer) or when family or personal medical history warrants. The ACMG does not recommend offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups, or the routine offering of Tier 4 panels.

TESTING STRATEGY

After testing the proband, targeted testing on the reproductive partner is preferred. Testing only applies to genes meeting criteria outlined above. If a lab does a more extensive test, then testing for other findings in the reproductive partner would not meet criteria. In general, carrier screening can be done once per lifetime. However, if only targeted or limited testing was done previously, then a more general non-targeted panel could be performed, particularly in cases where there is a new reproductive partner. In this case it is likely that genes could be re-tested.

Table PG1. American College of Medical Genetics and Genomics Tiered Approach to Carrier Screening3

<table>
<thead>
<tr>
<th>Tier</th>
<th>Screening Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cystic fibrosis + spinal muscular atrophy + risk based screening</td>
</tr>
<tr>
<td>2</td>
<td>≥1/100 carrier frequency + Tier 1</td>
</tr>
<tr>
<td>3</td>
<td>≥1/200 carrier frequency + Tier 2 (includes X-linked conditions)</td>
</tr>
<tr>
<td>4</td>
<td>&lt;1/200 carrier frequency + Tier 3 (genes and conditions will vary by laboratory)</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics

X-linked genes considered appropriate for carrier screening in Tier 3 include: ABCD1, AFF2, ARX, DMD, F8, F9, FMR1, GLA, L1CAM, MID1, NR0B1, OTC, PLP1, RPGR, RS1, and SLC6A8. Refer to Tables 1 through 5 in the ACMG position statement for additional details regarding appropriate autosomal recessive conditions and their associated carrier frequencies.

Carrier screening should only be performed in adults.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of 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 alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods. Carrier screening with appropriate genetic counseling is performed in adults.

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. It is being implemented for genetic testing medical protocol updates starting in 2017 (see Table PG2). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

The 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 PG3 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<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</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

Table PG3. American College of Medical Genetics and Genomics-Association for Molecular Pathology Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</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>
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MEDICARE ADVANTAGE

Because Medicare generally only covers tests that are medically necessary for diagnosis and treatment, screening services that are risk assessment testing may be considered **not medically necessary**.

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.

TARGETED CARRIER SCREENING

Carrier screening tests asymptomatic individuals in order to identify those who are heterozygous for serious or lethal single-gene disorders. The purpose of screening is to determine the risk of conceiving an affected child and “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, or personal or family history. Conditions selected for screening can be based on ethnicities at high-risk or may be panethnic. An example of effective ethnicity-based screening involves Tay-Sachs disease, with a 90% reduction in the disease following the introduction of carrier screening in the 1970s in the U.S. and Canada. An example of panethnic screening involves cystic fibrosis when the American College of Obstetricians and Gynecologists (ACOG) noted that ethnic intermarriage was increasing in the U.S. and recommended panethnic cystic fibrosis carrier screening in 2005.
NON-TARGETED CARRIER SCREENING

Non-targeted carrier screening involves screening individuals or couples for disorders in many genes (up to 100s) by next-generation sequencing. Non-targeted carrier screening panels may screen for diseases that are present with increased frequency in specific populations but also include a wide range of diseases for which the patient is not at increased risk of being a carrier. Arguments for non-targeted carrier screening include the potential to assess ethnicity, identify more potential conditions, efficiency, and cost. The conditions included in non-targeted carrier screening panels are not standardized and the panels may include many conditions not routinely evaluated and for which there are no existing professional guidelines.

This evidence review applies only if there is no separate evidence review 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.

Carrier screening for mitochondrial disorders associated with autosomal recessive inheritance of nuclear DNA variants is addressed in this review. Diagnostic genetic testing for mitochondrial disorders and carrier testing of known familial variants associated with mitochondrial disorders are addressed in the Genetic Testing for Mitochondrial Disorders Protocol.

REGULATORY STATUS

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

A number of commercially available genetic tests exist for carrier screening. They range from testing for individual diseases to small panels designed to address testing based on ethnicity as recommended by practice guidelines (ACOG, ACMG), to large non-targeted panels that test for numerous diseases.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.