FEP Medical Policy Manual

FEP 2.04.107 Carrier Screening for Genetic Diseases

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Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
2.04.116 - Invasive Prenatal (Fetal) Diagnostic Testing
2.04.117 - Genetic Testing for Mitochondrial Disorders
4.02.05 - Preimplantation Genetic Testing

Carrier Screening for Genetic Diseases

Description

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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.

OBJECTIVE

The objective of this evidence review is to evaluate whether targeted risk-based or non-targeted carrier screening panel testing improves the net health outcomes of individuals at either an increased risk or population risk of inherited X-linked or autosomal recessive single-gene disorders.

POLICY STATEMENT

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 carrier 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 a 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 (eg, *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

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. If targeted testing is performed by a panel, the most appropriate panel code available should be used. The panel and the panel billing code should include *CFTR* and *SMN1*. If the carrier screening test is a panel less than 15 genes and does not include *CFTR* or *SMN1*, but would be 15 or more genes if including *CFTR* or *SMN1*, coding should adhere to national medical coding guidelines.

Non-targeted carrier screening applies to persons of any risk including average risk. Non-targeted carrier screening must include the *CFTR* and *SMN1* genes. 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."[ACOG Committee Opinion No. 690; PMID: 28225425]

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.[Lazarin et al (2014); PMID: 25494330][Gregg et al (2021); PMID 34285390] 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.[Arjunan et al (2020); PMID: 32474937] 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. [Guo et al (2019); PMID: 30846881]

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.[Gregg et al (2021); PMID 34285390] 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 (eg, 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),[ACOG Committee Opinion No. 691; PMID: 28225426] to enhance communication and precision while advancing equity in carrier screening (see Table PG1).[Gregg et al (2021); PMID 34285390] The consensus group recognized no accepted standard in defining the severity of various conditions; and, based off previously published 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.[Lazarin et al (2014); PMID: 25494330]

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.[Guo et al (2019); PMID: 30846881] 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 frequency 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.[Gregg et al (2021); PMID 34285390]

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 Screening[a]

Tier	Screening Recommendations
1	Cystic fibrosis + spinal muscular atrophy + risk-based screening
2	≥1/100 carrier frequency + Tier 1
3	≥1/200 carrier frequency + Tier 2 (includes X-linked conditions)
4	<1/200 carrier frequency + Tier 3 (genes and conditions will vary by laboratory)

ACMG: American College of Medical Genetics and Genomics

[a] Adapted from Gregg AR et al (2021; PMID 34285390).

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. Additional details are available in the Supplemental Information section.

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 evidence review updates starting in 2017 (see Table PG2). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

The 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 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Some Plans may have contract or benefit exclusions for genetic testing.

Access to pregnancy termination services is subject to local state legislation.

FDA 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.

RATIONALE

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 ACOG 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists

In 2017 (reaffirmed in 2020), the American College of Obstetricians and Gynecologists (ACOG) made the following recommendations on expanded (i.e., non-targeted) carrier screening [16,]:

"Ethnic-specific, panethnic, 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 the 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.

The ACOG also noted that expanded carrier screening 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.

In 2015, a joint statement on expanded carrier screening was issued by ACOG, the American College of Medical Genetics and Genomics (ACMG), the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine.[2,] 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 expanded carrier screening 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:

- Screening for hemoglobinopathies requires use of mean corpuscular volume and hemoglobin electrophoresis.
- Tay-Sachs disease carrier testing has a low detection rate in non-Ashkenazi populations using molecular testing for the 3 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 expanded carrier screening. 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."

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."

American College of Medical Genetics and Genomics

In 2021, the ACMG issued a position statement on screening for autosomal recessive and X-linked conditions during pregnancy and preconception.[17,] This position statement replaces the 2013 ACMG position statement on prenatal and preconception expanded carrier testing, and incorporates ACOG Committee Opinion 691 recommendations.[7,]

The ACMG consensus group made the following recommendations:

- Replacing the term "expanded carrier screening" with "carrier screening" as no precise definition for "expanded" exists.
- Establishing a tier-based system of carrier screening, to enhance communication and precision while advancing equity in carrier screening (see Table 1 below).
- Carrier screening paradigms should be ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion.
- Offering Tier 3 carrier screening to all pregnant patients and those planning a pregnancy.
- 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.
- Consider offering Tier 4 screening 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.

- Routine offering of Tier 4 panels.

Table 1. American College of Medical Genetics and Genomics Tiered Approach to Carrier Screening[17,]

Tier	Screening Recommendations
1	Cystic fibrosis + spinal muscular atrophy + risk based screening
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3	≥1/200 carrier frequency + Tier 2 (includes X-linked conditions)
4	<1/200 carrier frequency + Tier 3 (genes and conditions will vary by lab)

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 for screening and their associated carrier frequencies.

The ACMG recommends the following components regarding laboratory reporting of carrier screening panels:

- The content of carrier screen panels and corresponding ACMG tier must be described.
- The testing approach and detectable variant types should be clearly stated.
- Not reporting residual risk estimates.
- Only reporting pathogenic and likely pathogenic variants.
- Interpretation should consider genes and variants with multiple disease associations.
- Reporting of a variant of uncertain significance (VUS) only in the partners of identified carriers and only with consent of the patient.

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 are in evidence reviews for each condition (see 2.04.02 and 2.04.80, respectively).

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy	Policy updated with literature review through August 5, 2022; Benefit Application section updated. Policy statements unchanged. New Benefit for FEP, new policy adopted.