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## Overview

Carrier screening is performed to identify genetic risks that could impact reproductive decision-making for parents or prospective parents. Carriers are generally not affected but have an increased risk to have a child with a genetic condition. Carrier screening may be available for autosomal recessive conditions, X-linked conditions, and certain chromosome abnormalities. Ideally, carrier screening is performed prior to pregnancy so that a full range of reproductive options are available to an at-risk couple. However, in practice, it is often performed early in pregnancy when prenatal care is established.

- This policy does not include prenatal or preimplantation genetic testing. Refer to policies on **Genetic Testing for Prenatal Screening and Diagnostic Testing** and **Preimplantation Genetic Diagnosis** for those purposes.
- In addition, testing that may identify carriers who have clinical signs and symptoms (e.g., cystic fibrosis testing for men with congenital absence of the vas deferens, fragile X genetic testing for women with premature ovarian failure) is addressed as **Diagnostic Genetic Testing of a Symptomatic Patient For Conditions Other Than Cancer**.

### Coverage guidelines

#### General coverage guidelines

Individuals may be considered for genetic testing for carrier screening when **ALL** of the following conditions are met:

- **Technical and clinical validity:** The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility:** Healthcare providers can use the test results to provide significantly better medical care and/or assist individuals with reproductive planning.
- **Reasonable use:** The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will only be considered for the number of genes or tests necessary to establish carrier status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Carrier testing will be allowed once per lifetime. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
- Carrier testing is indicated only in adults. Carrier screening in minor children is not indicated, except in the case of a pregnancy of the minor child.

#### Routine carrier screening

Individuals may be considered for routine carrier screening when testing is supported by evidence-based guidelines from governmental organizations and/or well-recognized professional societies in the United States.

Test-specific policy examples are available below for:

- [Cystic fibrosis](#)
- [Hemoglobinopathies](#) (alpha- and beta-thalassemia, sickle cell anemia)
- [Ashkenazi Jewish diseases](#)

#### Carrier screening based on family history

Individuals may be considered for carrier screening based on a family history of a genetic condition when **ALL** of the following conditions are met in addition to the general criteria above:

- The diagnosis of a genetic condition in a family member is known.
- The parent(s) or prospective parent(s) are at-risk to be carriers of that condition based on the pattern of inheritance.
- The genetic condition is associated with potentially severe disability or has a lethal natural history.

A test-specific policy example is available below for [fragile X syndrome](#).

### Partner testing of known carrier or affected individuals

Individuals may be considered for carrier screening if their partners are known carrier or affected individuals when all of the following conditions are met in addition to the general criteria above:

- The diagnosis of a genetic condition or carrier status in the partner is known.
- The genetic condition is associated with potentially severe disability or has a lethal natural history.

### Test-specific examples

#### Carrier screening for cystic fibrosis (CF)

The American College of Medical Genetics (ACMG) and the American College of Obstetrics and Gynecology (ACOG) have current practice guidelines regarding the use of CF carrier screening.<sup>1-4</sup> The ACMG guideline identifies 23 common pan-ethnic mutations that define the minimum standard for a mutation panel.<sup>4</sup> Many laboratories offer standard mutation panels (including all 23 core mutations), expanded mutation panels, and gene sequencing. The appropriate use of these technologies depends on the indication for testing.

Testing may be considered when ANY of the following are met:

- The standard CF mutation panel is considered for any individual planning a pregnancy or currently pregnant; OR
- Adults with a family history of CF:
  - If the familial mutation(s) are known and included in the standard mutation panel, then that test only is needed; OR
  - If the familial mutation(s) are not known or are not included in the standard mutation panel, then an expanded mutation panel can be considered; OR
- Individuals whose partners are known carriers of or affected with CF or congenital absence of the vas deferens (CAVD/CBAVD) are considered for testing with an expanded mutation panel or sequencing.

In our opinion, a standard mutation panel should include all 23 of the ACMG/ACOG recommended mutations and no more than 27 additional mutations, for a total of 50 or fewer mutations on the panel. These additional mutations may improve the detection rate for specific ethnic groups.

Panels that include >50 mutations should be considered expanded mutation panels and have more restricted use. They typically do not substantially increase the detection rate

#### References:

1. American College of Obstetricians and Gynecologists, American College of Medical Genetics. Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and laboratory guidelines. Washington, DC: ACOG, ACMG; 2001;1-32.
2. Committee on Genetics, American College of Obstetricians and Gynecologists. ACOG Committee Opinion. Number 325, December 2005. Update on carrier screening for cystic fibrosis. *Obstet Gynecol.* 2005;106(6):1465-8.

3. Grody WW, Cutting GR, Klinger KW, et al.; Subcommittee on Cystic Fibrosis Screening, Accreditation of Genetic Services Committee, ACMG. American College of Medical Genetics. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genet Med*. 2001;3(2):149-54. PDF available at: [http://www.acmg.net/AM/Template.cfm?Section=Policy\\_Statements&Template=/CM/HTMLDisplay.cfm&ContentID=4157](http://www.acmg.net/AM/Template.cfm?Section=Policy_Statements&Template=/CM/HTMLDisplay.cfm&ContentID=4157)
4. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med*. 2004;6(5):387-91. PDF available at: [http://www.acmg.net/StaticContent/StaticPages/CF\\_Mutation.pdf](http://www.acmg.net/StaticContent/StaticPages/CF_Mutation.pdf).

### Carrier screening for Ashkenazi Jewish diseases

Carrier screening is widely available for at least 11 genetic disorders that are more common and/or have superior mutation detection rates in the Ashkenazi Jewish population. The American College of Obstetrics and Gynecology (ACOG)<sup>1</sup> and the American College of Medical Genetics (ACMG)<sup>2</sup> recommend carrier screening for a group of disorders when at least one member of a couple is Ashkenazi Jewish and that couple is pregnant or planning pregnancy.

Both organizations agree that testing should be offered for cystic fibrosis, Canavan disease, familial dysautonomia, and Tay-Sachs disease. ACMG also recommends routine testing for Fanconi anemia, Niemann-Pick disease, Bloom syndrome, mucopolysaccharidosis IV, and Gaucher disease.<sup>2</sup> Maple syrup urine disease and glycogen storage disease 1a carrier screening for common Ashkenazi Jewish mutations is now clinically available, but not addressed in current carrier screening guidelines. These two tests meet the criteria for additional carrier screening set in the 2008 ACMG guidelines.<sup>2</sup>

Testing may be considered for carrier screening for **all or any desired subset** of the Ashkenazi Jewish genetic diseases when BOTH of the following are met:

- The individual is planning a pregnancy or currently pregnant; AND
- At least one partner of a couple is Ashkenazi Jewish
  - NOTE: Detection rates for testing are higher in people with Ashkenazi Jewish ancestry. If only one partner of a couple is Ashkenazi Jewish, testing should start in that person when possible.

Testing may be considered for carrier screening of a **single** Ashkenazi Jewish disease if EITHER of the following are met:

- The individual has a family history of one of these conditions; OR
- The individual's partner is a known carrier or affected with any of these conditions

#### References:

1. Committee on Genetics, American College of Obstetricians and Gynecologists. ACOG Committee Opinion, Number 442, October 2009. Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. *Obstet Gynecol*. 2009;114(4):950-3.
2. Gross SJ, Pletcher BA, Monaghan KG; ACMG Professional Practice and Guidelines Committee. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med*. 2008;10(1):54-6.

### Carrier screening for hemoglobinopathies

Hemoglobinopathies include genetic changes in the alpha- and beta-globin genes, which cause alpha-thalassemia, beta-thalassemia, sickle cell anemia, and other less common blood disorders. The American College of Obstetricians and Gynecologists (ACOG) states that carrier screening for hemoglobinopathies is appropriate for people with African, Mediterranean, and/or Southeast Asian ancestry who are pregnant or planning a pregnancy.<sup>1</sup> However, they note that carrier frequencies may be higher in some other ethnic populations as well.<sup>1</sup>

Hemoglobinopathy screening by red blood cell indices (complete blood count) and quantitative hemoglobin analysis may be considered when ANY of the following are met:

- The individual is planning a pregnancy or currently pregnant AND at least one member of the couple is in an at-risk population. (This includes but may not be limited to people of African, Southeast Asian, and/or Mediterranean ancestry.); OR
- The individual has a family history of a hemoglobinopathy; OR
- The individual's partner is a known carrier or affected with a hemoglobinopathy.
- The individual is participating in college athletics, military training, or other strenuous activity in which a carrier may become symptomatic.

Molecular genetic testing may be considered when ANY of the following are met:

- The individual is known or suspected to be a carrier of a hemoglobinopathy based on the results of red blood cell indices and hemoglobin analysis, and/or ethnic background and family history AND mutation confirmation is needed to verify carrier status, or for consideration of preimplantation or prenatal diagnosis; OR
- The individual has a family history of a hemoglobinopathy and the familial mutations are known

Reference: ACOG Practice Bulletin, Number 78, January 2007. Hemoglobinopathies in pregnancy. *Obstet Gynecol.* 2007;109(1):229-37.

### Fragile X carrier testing

Fragile X syndrome is the most common inherited cause of mental retardation. Guidelines from the American College of Obstetricians and Gynecology (ACOG)<sup>1</sup>, the American College of Medical Genetics (ACMG)<sup>2</sup>, the American Society for Reproductive Medicine (ASRM)<sup>3</sup>, and the National Society of Genetic Counselors (NSGC)<sup>4</sup> support fragile X carrier testing in adults with a family history of mental retardation or a known family history of fragile X syndrome.

Testing may be considered when EITHER of the following are met:

- The individual has a known family history of fragile X syndrome; OR
- The individual has a family history of mental retardation of unknown cause.

### References:

1. ACOG Committee Opinion, Number 338, June 2006. Screening for fragile X syndrome. *Obstet Gynecol.* 2006;107:1483-5.
2. Sherman, S., Pletcher, BA, and Driscoll, DA. ACMG Practice Guideline. Fragile X syndrome: Diagnostic and carrier testing. *Genet Med.* 2005;7(8):584-7.
3. American Society of Reproductive Medicine (February 2008). Indications for Fragile X Mental Retardation (FMR-1) Genetic Testing. White paper.
4. McConkie-Rosell A, Finucane B, Cronister A, Abrams L, Bennett RL, Pettersen BJ. Genetic counseling for fragile X syndrome: updated recommendations of the National Society of Genetic Counselors. *J Genet Counsel.* 2005; 14(4):249-70.

## Exclusions

### Multiplex Carrier Screening

Multiplex [carrier screening](#) tests are designed to identify carrier status or predict risk for many [genetic](#) diseases (70 or more) in a single test. Several multiplex carrier screening tests are available now. Others are known to be in development and will come to market in the next few years. Each test has a unique set of diseases included in novel and proprietary genetic testing platforms.

Of the genetic conditions included in the currently available multiplex carrier screening tests, 12 of them are recommended for at least some people based on ethnicity by either the American College of Obstetrics and Gynecology (ACOG) and/or the American College of Medical Genetics (ACMG).<sup>3-8</sup> However, mutation analysis is not the preferred initial screening test for some.

These tests do not meet the criteria above for technical and clinical validity and clinical utility:

- The technologies used by the multiplex carrier screening tests are novel. Information about the test's performance, if available, is often provided completely by the laboratory marketing the test, which could be subject to bias.
- Some of the commonly included tests, such as beta-thalassemia and Tay-Sachs disease, have inexpensive and reliable screening tests available (CBC with RBC indices and hexosaminidase A [enzyme](#) activity, respectively) that are superior to genetic testing.
- Multiplex carrier screening tests typically include carrier screening for many diseases that have not been identified as appropriate for population-based carrier screening. They may also include disorders, such as [hereditary hemochromatosis](#) and factor V Leiden, which affect primarily adults and are generally manageable. These kinds of conditions do not meet the requirements for reproductive carrier screening programs.