

# Protocol

## Carrier Testing for Genetic Diseases

(204107)

Medical Benefit	Effective Date: 04/01/14	Next Review Date: 01/15
Preauthorization	Yes	Review Dates: 01/14

*The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** 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.*

### Description

Carrier testing 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 the gene mutation to their offspring. Carrier testing may be performed before conception or during a pregnancy. This concept policy offers a framework for evaluating the utility of carrier genetic testing.

### Background

#### Purpose

The purpose of this Protocol is to provide assistance in evaluating the utility of carrier testing for genetic diseases. In providing a framework for evaluating these tests, this Protocol will not attempt to determine the clinical utility of carrier testing for specific disorders. Rather, it provides guidelines that can be applied to a wide range of different tests.

This Protocol applies only if there is not a separate Protocol that outlines specific criteria for carrier testing. If a separate Protocol does exist, then the criteria for medical necessity in that Protocol supersede the guidelines in this Protocol.

#### 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 a particular population, or based on family history.

Panethnic screening (population screening) for carrier status is done for single-gene disorders that are common in the population.

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.

#### Expanded carrier screening (ECS)

New technologies have made it possible to screen for mutations in many genes more efficiently than testing mutations in a single gene or a small number of population-specific mutations in several genes. Commercial laboratories offer these expanded carrier screening panels, which is defined as a non-targeted approach to carrier screening. There is no standardization to the makeup of these genetic panels, the composition of the

panels varies among labs, and different commercial products for the same condition may test a different set of genes. Although ECS panels may include conditions that are routinely assessed in carrier testing, these ECS panels include many conditions that are not routinely evaluated and for which there are no existing professional guidelines.

### *Definitions*

**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. When associated with an autosomal recessive or X-linked disorder, carriers of the causative mutation are typically unaffected. When associated with an autosomal dominant disorder, the individual has one normal and one mutated copy of the gene and may be affected with the disorder, may be unaffected but at high risk of developing the disease later in life, or the carrier may remain unaffected because of the sex-limited nature of the disease. Homozygous-affected offspring (those who inherit the mutation from both parents) manifest the disease.

**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:** Genetic testing involves the analysis of chromosomes, DNA (deoxyribonucleic acid), RNA (ribonucleic acid), 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 causing 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 (for example, if the individual has a disease-causing mutation that wasn't included in the test assay).

### *Regulatory Status*

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

There are a number of commercially available genetic tests for carrier screening, which 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 [ACMG]), to large expanded panels that test for numerous diseases beyond those recommended in practice guidelines. The following is not a comprehensive list of some of the available panels:

**Counsyl™** (Counsyl) tests for more than 100 diseases, which, according to their 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 cystic fibrosis 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 the hemoglobinopathies, Fragile X syndrome, cystic fibrosis, metabolic disorders, and others.

Inherigen™ (GenPath) is a pan-ethnic test for over 160 inherited diseases that are disorders that are typically childhood onset with severe symptoms, such as immunodeficiencies, and several metabolic diseases, including Tay-Sachs disease, glycogen storage diseases and fatty acid oxidation disorders. InheriGen Plus includes all InheriGen diseases plus cystic fibrosis, spinal muscular atrophy and Fragile X syndrome.

Inheritest™ (LabCorp) is 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 the ACMG-recommended tests for carrier screening, plus Fragile X syndrome, sickle cell anemia, hemoglobin C trait and spinal muscular atrophy.

### Policy (Formerly Corporate Medical Guideline)

Carrier testing for genetic diseases is considered **medically necessary** when one of the following criteria is met:

- The individuals have a previously affected child with the genetic disease OR
- One or both individuals have a first- or second-degree relative who is affected OR
- One or both individuals have a first-degree relative with an affected offspring 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 (see policy guidelines\*)

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 in the homozygous or compound heterozygous state.
- 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 sensitivity and specificity to guide clinical decision making and residual risk is understood. (see policy guidelines\*\*)
- An association of the marker with the disorder has been established.

In all other situations carrier testing would be considered investigational.

Expanded carrier screening panels are considered to be **not medically necessary**. (See policy guidelines\*\*\*)

### Policy Guideline

\*If there is no family history of or ethnic predilection for a disease, carrier screening is not recommended if the carrier rate is < 1% in the general population.

\*\*The American College of Medical Genetics (ACMG) recommends testing for specific mutations which will result in a carrier detection rate of  $\geq 95\%$  for most disorders.

\*\*\*The ACMG defines expanded panels as those that use next-generation sequencing to screen for mutations in many genes, as opposed to gene-by-gene screening (e.g., ethnic-specific screening or panethnic testing for cystic fibrosis). An ACMG position statement states that although commercial laboratories offer expanded carrier screening panels, there has been no professional guidance as to which disease genes and mutations to include.

(1)

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

Carrier testing should only be performed in adults.

Some examples of populations in which the carrier frequency is thought to exceed the threshold that is appropriate for carrier screening are:

#### Ashkenazi Jewish

The ACMG and the American College of Obstetricians and Gynecologists (ACOG) both recommend carrier screening for Ashkenazi Jewish individuals for:

- Tay-Sachs disease (disease incidence 1/3000; carrier frequency 1/30),
- Canavan disease (1/6,400; 1/40), and
- cystic fibrosis (1/2,500-3,000; 1/29) and
- familial dysautonomia (1/3,600; 1/32)

In addition, the ACMG recommends that the following also be offered to all individuals of Ashkenazi Jewish descent who are pregnant, or considering pregnancy:

- Fanconi anemia (group C) (1/32,000; 1/89), and
- Niemann-Pick (type A) (1/32,000; 1/90), and
- Bloom syndrome (1/40,000; 1/100), mucopolidosis IV (1/62,500; 1/127), and
- Gaucher disease (1/900; 1/15).

#### Hemoglobinopathies

In 2007, ACOG issued guidelines for hemoglobinopathies in pregnancy, which included recommendations for carrier screening. (2) For carrier screening, ACOG recommends that individuals of African, Southeast Asian and Mediterranean descent are at risk for being carriers of hemoglobinopathies and should be offered carrier screening and, if both parents are determined to be carriers, genetic counseling.

#### Cystic Fibrosis

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive condition in the non-Hispanic white population. Carrier rates are one in 24 in the Ashkenazi Jewish population and one in 25 in the non-Hispanic white general population.

In 2011, ACOG issued an update on carrier screening for CF and the Committee on Genetics concluded that it is important that CF screening continues to be offered to women of reproductive age, and that because it is difficult to assign a single ethnicity to individuals, it is reasonable to offer CF carrier screening to all patients.

Current guidelines, revised by the ACMG in 2004, use a 23-mutation panel and were developed after assessing the initial experiences upon implementation of CF screening into clinical practice. Using the 23-mutation panel, the detection rate is 94% in the Ashkenazi Jewish population and 88% in the non-Hispanic white general population.

#### *General Principles*

This Protocol is largely based on the general principles of carrier testing and accepted practice guidelines from major medical societies.

The test should be cleared or approved by the U.S. Food and Drug Administration (FDA), or performed in a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory.

Ideally, peer-reviewed literature on the performance and indications for the test should be available. The evaluation of a genetic test focuses on three main principles: 1) analytic validity (the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); 2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and 3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

The analytic validity of many of the targeted carrier screening tests has been reported to be high. For example, one major laboratory reports that the analytic validity of their cystic fibrosis (CF) 32-mutation panel and their Ashkenazi Jewish panel (which includes testing for eight conditions, as recommended by ACMG plus CF) is 99% (3)

For expanded carrier screening panels, the analytic validity is either unknown (no published data) or cannot be adequately assessed due to weaknesses in assay validation.

The clinical validity of carrier screening is difficult to assess because there is no gold standard for carrier status that can be used in determining clinical validity of carrier testing. Carriers are by definition asymptomatic for the diseases being tested, and thus the association of the genetic defect with the disorder (carrier state) is not possible to define. In particular, it would not be possible to determine whether a negative test is a false-negative or a true-negative result due to the inability to define the carrier state in clinical terms.

The clinical utility of carrier testing is in how the results of the diagnostic test will have an impact on management decisions and health outcomes. Changes in management will involve decisions on family planning. The results of genetic testing can be used to assist individuals with reproductive decisions such as avoidance of pregnancy, preimplantation genetic testing, adoption, etc. The beneficial health outcome would be a reduction in the prevalence of severe, recessive inherited disorders among live births in patients who get tested. For tests that have high accuracy in detecting pathologic mutations, and very low false-positive rates, it is likely that use of the test will reduce the number of births with the inherited disorder. The magnitude of benefit will depend on the frequency of the disorder and the sensitivity of the test in detecting mutations that are present.

Carrier testing should be performed for diseases that have high penetrance and do not have (a highly) variable expression.

Carrier testing is only appropriate when the individual(s) are planning a pregnancy or are currently pregnant.

Population screening should only be performed if the disease prevalence is high and the morbidity of the disease is high.

#### *Expanded carrier screening panels*

Expanded carrier screening (ECS) panels may provide the opportunity to test carriers for a greatly expanded number of diseases for a lower cost than the conventional forms of carrier testing. However, the current limitations of these expanded panels include technical and interpretive limitations and ethical and genetic counseling challenges.

#### *Genetic counseling*

The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, most or all genetic testing for heritable conditions should be preceded by genetic counseling so that the patient is well informed about the pros and cons of genetic testing, is able to provide informed consent, and, if it is performed, what the potential impact of the information could be on the patient and on his or her family.

### Medicare Advantage

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

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

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4. Bell CJ, Dinwiddie DL, Miller NA et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. *Sci Transl Med* 2011; 3(65):65ra4.
5. Lizarin GA, Haque IS, Nazareth S et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *Genet Med* 2013; 15(3):178-86.
6. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003; 168(7):818-900.
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10. Gross SJ, Pletcher BA, Monaghan KG. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med* 2008; 10(1):54-6.
11. Title XVIII of the Social Security Act, Section 1862(a)(1)(A), regarding coverage for items or services which are not reasonable and necessary for the diagnosis and treatment of illness or injury.