Protocol

Carrier Testing for Genetic Diseases

(204107)

Medical Benefit		**Effective Date**: 04/01/14	**Next Review Date**: 11/17
Preauthorization	Yes	**Review Dates**: 01/14, 01/15, 11/15, 11/16	

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.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic but at risk for having an offspring with a genetic disease	Interventions of interest are: • Carrier testing	Comparators of interest are: • No carrier testing	Relevant outcomes include: • Test accuracy • Test validity • Changes in reproductive decision making
Individuals: • Who are asymptomatic but at risk for having an offspring with a genetic disease	Interventions of interest are: • Expanded carrier testing	Comparators of interest are: • Conventional carrier testing	Relevant outcomes include: • Test accuracy • Test validity • Changes in reproductive decision making

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

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. Results of genetic testing can be used to assist individuals with reproductive decisions such as avoidance of pregnancy, preimplantation genetic testing, and adoption. Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for expanded carrier testing in individuals who are asymptomatic but at risk for having an offspring with a genetic disease includes mutation prevalence studies; direct evidence is lacking. Relevant outcomes are

test accuracy, test validity, and changes in reproductive decision making. Analytic validity of expanded carrier screening panels is unknown. These panels have significant limitations, including increased false positives and variants of uncertain significance due to testing for many mutations, false negatives due to rare mutations not included in panel testing, the inclusion of diseases with decreased penetrance and variable expressivity, and difficulties with communicating residual risk and actionability of information obtained. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

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 clinical validity 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 Guidelines

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

**The American College of Medical Genetics and Genomics (ACMG) recommends testing for specific mutations which will result in a carrier detection rate of 95% or higher 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 (Grody et al, 2013).

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.

Examples of populations in which the carrier frequency is thought to exceed the threshold that is appropriate for carrier screening follow.

Ashkenazi Jewish Populations

The ACMG and the American College of Obstetricians and Gynecologists (ACOG) both recommend carrier screening for Ashkenazi Jewish individuals for (ACOG No. 442, 2009):

- Tay-Sachs disease (disease incidence 1/3,000; carrier frequency 1/30), and
- 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), and
- mucolipidosis IV (1/62,500; 1/127), and
- Gaucher disease (1/900; 1/15).

Hemoglobinopathies

In 2013, ACOG reaffirmed a 2007 practice bulletin for hemoglobinopathies in pregnancy, which included recommendations for carrier screening. (American Family Physician, 2007; ACOG No. 78, 2013). For carrier screening, individuals of African, Southeast Asian, and Mediterranean descent are at risk for being carriers of hemoglobinopathies; ACOG recommends that individuals from these ethnic groups 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 to continue offering CF screening to women of reproductive age, and, because it is difficult to assign a single ethnicity to individuals, it is reasonable to offer CF carrier screening to all patients (ACOG No. 486, 2011).

Current guidelines, revised by the ACMG in 2004 (Watson et al, 2004) and reaffirmed in 2013, 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.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is the second most common fatal autosomal recessive disorder after CF, with an estimated carrier frequency of 1/40 to 1/60 in the general population (Prior, 2008). SMA affects alpha motor neurons in the spinal cord; degeneration of these neurons leads to severe, progressive proximal muscle weakness. Based on age of onset and clinical course, three phenotypes are observed: In type 1 SMA (Werdnig-

Hoffmann), severe, generalized muscle weakness and hypotonia are present at birth or within three months, and death from respiratory failure usually occurs before age two years. In type 2 SMA, children can sit, although they are unable to stand or walk unaided; survival is typically beyond age four years. Type 3 SMA (Kugelberg-Welander) is a milder form – patients can walk unaided – with onset during infancy or youth. There is no effective treatment for SMA (ACOG No. 432, 2009).

Recommendations from ACMG and ACOG for SMA carrier testing differ. ACMG's 2008 guideline, reaffirmed in 2013, recommends carrier testing for SMA in all couples regardless of race or ethnicity. ACOG's 2009 Committee on Genetics opinion statement does not recommend SMA carrier screening in the general population. Rather, carrier screening may be offered to (1) those with a family history of SMA or SMA-like disease, and (2) those who request SMA carrier screening and have completed genetic counseling to review sensitivity, specificity, and limitations of screening (ACOG No. 432, 2009). ACOG opinion authors cited genetic complexity of SMA and the lack of pilot studies to determine best practices for pre- and post-test education and counseling for SMA screening.

General Principles of Carrier Screening for Genetic Diseases

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

Carrier genetic tests 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).

Analytic Validity: 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%.[1] 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.

Clinical Validity: The clinical validity of carrier screening is difficult to assess because there is no criterion 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.

Clinical Utility: The clinical utility of carrier testing is in how the results of the diagnostic test will impact management decisions and health outcomes. Changes in management will 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, or adoption. 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 (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 disease morbidity 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

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.

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**.

Background

The purpose of this evidence review is to assist in evaluating the utility of carrier testing for genetic diseases. It provides (1) a framework for evaluating these tests and (2) guidelines that can be applied to a wide range of different tests.

This Protocol applies only if there is no separate Protocol that outlines specific criteria for carrier testing. If a separate Protocol exists, then criteria for medical necessity in that Protocol supersede the guidelines herein.

Specific Patient Populations

Carrier screening may be performed for conditions found in the general population (pan-ethnic), for diseases more common in particular populations, or based on family history.

Pan-ethnic (population) screening for carrier status is done for single-gene disorders 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 descend 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

New technologies have made it possible to screen for mutations in many genes more efficiently than testing for mutations in a single gene or a small number of population-specific mutations in several genes. Commercial laboratories offer expanded carrier screening (ECS) panels, which comprise a nontargeted approach to carrier screening. There is no standardization to the makeup of these gene panels; panel composition varies among labs; and different commercial products for a single condition may test different sets of genes. Although ECS

panels may include conditions that are routinely assessed in carrier testing, ECS panels include many conditions 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 by the disorder, may be unaffected but at high risk of developing the disorder later in life, or the carrier may remain unaffected because of the sex-limited nature of the disorder. Homozygous-affected offspring (those who inherit the mutation from both parents) 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

Genetic testing involves the analysis of chromosomes, DNA, RNA, genes, or gene products to detect inherited (germline) or noninherited (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).

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. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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 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 descent panel, fragile X syndrome, a 100-mutation cystic fibrosis (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 testing for hemoglobinopathies, fragile X syndrome, CF, metabolic disorders, and others.

InheriGen™ (GenPath) is a pan-ethnic test for over 160 inherited disorders, typically those with childhood onset and severe symptoms, such as immunodeficiencies and several metabolic diseases, such as Tay-Sachs disease, glycogen storage diseases, and fatty acid oxidation disorders. InheriGen Plus includes all InheriGen diseases plus CF, spinal muscular atrophy (SMA), 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 ACMG-recommended tests for carrier screening, plus fragile X syndrome, sickle cell anemia, hemoglobin C trait, and SMA.

Natera Horizon has five different panels that screen for as few as four 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 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 [nine 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.

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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