

(204107)

(Formerly Carrier Testing for Genetic Diseases)

Medical Benefit		Effective Date: 04/01/18	Next Review Date: 11/18
Preauthorization	Yes	Review Dates: 01/14, 01/15, 11/15, 11/16, 11/17	

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: <ul style="list-style-type: none"> Who are asymptomatic but at risk for having an offspring with inherited single-gene disorders 	Interventions of interest are: <ul style="list-style-type: none"> Risk-based carrier screening 	Comparators of interest are: <ul style="list-style-type: none"> No carrier screening 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Changes in reproductive decision making
Individuals: <ul style="list-style-type: none"> Who are asymptomatic but at risk for having an offspring with inherited single-gene disorders 	Interventions of interest are: <ul style="list-style-type: none"> Expanded carrier screening 	Comparators of interest are: <ul style="list-style-type: none"> Risk-based carrier screening 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Changes in reproductive decision making

Description

Carrier screening is performed to identify individuals at risk of having offspring with inherited 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 inherited single-gene disorders who receive risk-based carrier screening, the evidence includes studies supporting analytic validity, clinical validity, and clinical utility. 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. 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 a meaningful improvement in the net health outcome.

For individuals who are asymptomatic but at risk for having offspring with inherited single-gene disorders who receive expanded carrier screening (ECS), the evidence includes studies on analytic validity, clinical validity, and indirectly clinical utility. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision

making. The analytic validity of ECS panels will depend on the molecular method used; two identified studies support the analytic validity for ECS, but variant ascertainment with next-generation sequencing requires careful evaluation. Three studies have found that ECS identifies more carriers and potentially affected fetuses. However, evidence to support the clinical validity of ECS beyond risk-based recommendations is limited and accompanied by some concerns including: interlaboratory agreement of variant pathogenicity assessment when sequencing identifies rare variants, the validity of disease severity classifications for rare disorders, and the certainty of predicted risk that the offspring will be affected by a severe phenotype for all the disorders included in a panel. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Carrier screening for genetic diseases is considered **medically necessary** 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 (see Policy Guidelines A)

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.

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 B)
- An association of the marker with the disorder has been established.

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

Expanded carrier screening panels are considered **investigational**. (See Policy Guidelines C)

Policy Guidelines

- A. If there is no family history of risk based or ethnic predilection for a disease carrier screening is not recommended when the carrier rate is less than 1% in the general population.
- B. The American College of Medical Genetics and Genomics (ACMG) recommends testing for specific variants which will result in a carrier detection rate of 95% or higher for most disorders.
- C. The ACMG defines 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). A 2013 ACMG position statement noted that, although commercial laboratories offer expanded carrier screening panels, there has been no professional guidance as to which disease genes and variants to include (Grody et al, 2013). The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 690 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 one 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, 2017).

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.

The evaluation of a genetic carrier screening test focuses on three main principles: (1) analytic validity (the technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (the performance characteristics of a test [sensitivity, specificity, positive and negative predictive values] in predicting incident disease [i.e., must take into account penetrance and expressivity as well as condition severity]); and (3) clinical utility (i.e., demonstrating that the information can be used to inform reproductive decisions).

Analytic Validity

The analytic validity of many targeted carrier screening tests has been reported to be high. For example, one major laboratory has reported that the analytic sensitivities and specificities of its CF 165-variant panel and their Ashkenazi Jewish panel (which includes testing for 51 variants and 16 conditions) are all 99% (both approved by the New York State Department of Health).⁷ Depending on the population and disease, not all risk-based carrier screening relies on testing for genetic variants—e.g., the Hexosaminidase A Enzyme Assay for Tay-Sachs disease or screening for hemoglobinopathies. The analytic validity of these tests performed in Clinical Laboratory Improvement Amendments (CLIA)-or College of American Pathologists (CAP)-certified labs is anticipated to be high. For genetic assays of pathogenic variants in risk-based carrier screening, analytic validity is similarly anticipated to be high.

Clinical Validity

The clinical validity of a carrier screening test is evaluated by its ability to predict carrier status. Clinical validity is influenced by carrier prevalence, penetrance, expressivity, and environmental factors.¹ Different variants in the same gene can result in different phenotypes (allelic heterogeneity) in most genetic disorders and impact clinical validity. Depending on the assay method (e.g., next-generation sequencing [NGS], microarray), clinical sensitivity and predictive values vary according to the proportion of known pathogenic variants evaluated. For example, clinical sensitivities for disorders in the previously mentioned Jewish panel ranged from 90% to 99% for all but Usher syndrome type 1F (62%).⁷ Clinical sensitivity will vary according to the number of known variants tested. Additionally, not all testing strategies rely solely on genetic testing—e.g., biochemical testing (hexosaminidase A) may be the initial test to screen for Tay-Sachs carrier status and blood counts for hemoglobinopathies. Finally, following a negative carrier screening test, the estimated residual risk of being a carrier reflects both the pretest probability (e.g., estimated carrier prevalence in the population) and clinical validity (test clinical sensitivity and specificity). Consequently, limitations in clinical validity are quantified in residual risk estimates.

Clinical Utility

The clinical utility of carrier screening is defined by the extent to which reproductive decision making or choices are informed (i.e., increases “reproductive autonomy and choice”¹). Evidence to support the clinical utility carrier screening for conditions with the highest carrier rates (e.g., Tay-Sachs disease, CF) among specific ethnic

groups is robust concerning the effect on reproductive decision making.^{3, 8-10} For example, early studies of Tay-Sachs carrier screening in Ashkenazi Jews demonstrated a marked impact on reproductive decisions^{8, 10} and, after some four decades of ethnicity-based carrier screening, most Tay-Sachs disease cases occur in non-Jewish individuals.⁹ As another example, a 2014 systematic review of CF carrier screening found that while individual carrier status “did not affect reproductive intentions or behaviors,” most couple carriers terminated affected fetuses.¹¹ For inherited single-gene disorders where carrier rates are of similar magnitude, recommendations to offer screening have therefore arguably a convincing rationale, even if partially based indirectly on results from other conditions.

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 PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUMAN Genome Organization (HUGO). The American College of Medical Genetics and Genomics (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 PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. 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 PG2. ACMG-AMP 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

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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.

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

Inherited Recessive Disorders

There are more than 1300 inherited recessive disorders (autosomal or X-linked) that affect 30 out of every 10,000 children.¹ Some diseases have limited impact on either length or quality of life, while others are uniformly fatal in childhood.

Carrier Screening

Carrier screening is testing asymptomatic individuals to identify those who are heterozygous for serious or lethal single-gene disorders with the purpose of informing the risk of conceiving an affected child “to provide ... information to optimize pregnancy outcomes based on ... personal preferences and values.”² Risk-based carrier screening is performed in individuals having an increased risk based on population carrier prevalence, and personal or family history. Conditions selected for screening can be based on ethnicities at high risk (e.g., Tay-Sachs disease in Ashkenazi Jews) or may be pan-ethnic (e.g., screening for cystic fibrosis carriers). Ethnicity-based screening for some conditions has been offered for decades and, in some cases, has reduced the prevalence of diseases. For example, a 90% reduction in Tay-Sachs disease followed introduction carrier screening in the 1970s in the United States and Canada.³ In addition, the U.S. population has become increasingly ethnically intermarried^{4,5}—a phenomenon the American College of Obstetricians and Gynecologists noted when offering a recommendation in 2005 for pan-ethnic cystic fibrosis carrier screening.⁶

While methods for carrier screening of conditions individually may have been onerous in the past, contemporary molecular techniques including next-generation sequencing allow simultaneously identifying carriers of a wide range of disorders efficiently and inexpensively.

Expanded Carrier Screening

Expanded carrier screening (ECS) involves screening individuals or couples for disorders in many genes (up to 100s). The disorders included may also span a range of disease severity or phenotype. Arguments for ECS include potential issues in assessing ethnicity, ability to identify more potential conditions, efficiency, and cost. Uncertain are the possible downsides of screening individuals at low risk, including a potential for incorrect variant ascertainment and the consequences of screening for rare single-gene disorders in which the likely phenotype may be uncertain (e.g., due to variable expressivity and uncertain penetrance). The list of conditions included in ECS panels is not standardized. Although ECS panels would include conditions assessed in risk-based screening, ECS panels include many conditions not routinely evaluated and for which there are no existing professional guidelines.

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

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 Amendments (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.

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 (American College of Obstetricians and Gynecologists, American College of Medical Genetics and Genomics), to large expanded panels that test for numerous diseases.

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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