Protocol

Carrier Screening for Genetic Diseases

(204107)

Medical Benefit		**Effective Date**: 04/01/18	**Next Review Date**: 11/20
Preauthorization	Yes	**Review Dates**: 01/14, 01/15, 11/15, 11/16, 11/17, 11/18, 11/19	

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 inherited single-gene disorder	Interventions of interest are: • Targeted risk-based carrier screening	Comparators of interest are: • No carrier screening	Relevant outcomes include: • Test validity • Changes in reproductive decision making
Individuals: • Who are either at increased risk or population risk of having offspring with an inherited recessive genetic disorder	Interventions of interest are: • Expanded carrier screening	Comparators of interest are: • Targeted risk-based carrier screening	Relevant outcomes include: • Test validity • Changes in reproductive decision making

DESCRIPTION

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.

SUMMARY OF EVIDENCE

For individuals who are asymptomatic but at risk for having offspring with an inherited 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 a meaningful improvement in the net health outcome.

For individuals who are either at increased risk or population risk for having offspring with an inherited recessive genetic disorder who receive expanded carrier screening, 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 expanded carrier screening identifies more carriers and more potentially affected fetuses. However, evidence to support the clinical validity of expanded carrier screening beyond risk-based recommendations

is limited and accompanied by some concerns regarding interlaboratory inconsistency of variant pathogenicity assessment, the validity of disease severity classifications for rare disorders, and uncertainty 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) has recommended testing for specific variants which will result in a carrier detection rate of 95% or higher for most disorders.

C. 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 (e.g., ethnic-specific screening or pan-ethnic 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 screening should only be performed in adults.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Risk-Based Condition-Specific Screening Recommendations

The American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics and Genomics (ACMG) have issued numerous guidelines on targeted risk-based screening (see Table 2).

Table 2. ACOG and ACMG Recommendations for Targeted Risk-Based Screening

Society	Recommendation	Year
Cystic fibrosis[a]		
ACOG	"Cystic fibrosis carrier screening should be offered to all women considering pregnancy or are pregnant."[9]	2017
ACMG	Current ACMG guidelines use a 23-variant panel and were developed after assessing the initial experiences on implementation of cystic fibrosis screening into clinical practice. Using the 23-variant panel, the detection rate is 94% in the Ashkenazi Jewish population and 88% in the non-Hispanic white general population.[10]	2013
Spinal muscular atrophy[b]		
ACOG	"Screening for spinal muscular atrophy should be offered to all women considering pregnancy or are pregnant. In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, SMN1 deletion testing should be recommended for the low-risk partner."[9]	2017
ACMG	Because spinal muscular atrophy is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity.[11]	2013
Tay-Sachs disease		
ACOG	"Screening for Tay-Sachs disease should be offered when considering pregnancy or during pregnancy, if either member of a couple is of Ashkenazi Jewish, French-Canadian, or Cajun descent. Those with a family history consistent with Tay-Sachs disease should also be screened."[9]	2017
Fragile X syndrome		
ACOG	"Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant. If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an FMR1 premutation."[9]	2017

ACMG: American College of Medical Genetics and Genomics; ACOG: American College of Obstetricians and Gynecologists.
[a] Carrier rates: Ashkenazi Jews 1/24, non-Hispanic white 1/25, Hispanic white 1/58, African American 1/61, Asian American 1/94.
[b] General population carrier rate: 1/40 to 1/60.

TARGETED RISK-BASED CARRIER SCREENING

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a

clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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%).[8] 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.[3,13-15] For example, early studies of Tay-Sachs carrier screening in Ashkenazi Jews demonstrated a marked impact on reproductive decisions[13,15] and, after some four decades of ethnicity-based carrier screening, most Tay-Sachs disease cases occur in non-Jewish individuals.[14] 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.[16] For inherited single-gene disorders where carrier rates are of similar magnitude, recommendations to offer screening have a convincing rationale, even if partially based indirectly on results from other conditions. One caveat is that family history, ethnicity, and race are self-reported, and may not be completely accurate, particularly in multi-ethnic and multi-racial societies.[17]

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 protocol 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, screening services that are risk assessment testing may be considered **not medically necessary**.

BACKGROUND

INHERITED RECESSIVE DISORDERS

There are more than 1,300 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.

Targeted Carrier Screening

Carrier screening tests asymptomatic individuals in order to identify those who are heterozygous for serious or lethal single-gene disorders. The purpose of screening is to determine the risk of conceiving an affected child and "to optimize pregnancy outcomes based on … personal preferences and values."[2] Risk-based carrier screen-

ing is performed in individuals having an increased risk based on population carrier prevalence, or personal or family history. Conditions selected for screening can be based on ethnicities at high-risk or may be pan-ethnic. An example of effective ethnicity-based screening involves Tay-Sachs disease, with a 90% reduction in the disease following the introduction of carrier screening in the 1970s in the U.S. and Canada.[3] An example of pan-ethnic screening involves cystic fibrosis when the American College of Obstetricians and Gynecologists noted that ethnic intermarriage was increasing in the U.S.[4,5] and recommended pan-ethnic cystic fibrosis carrier screening in 2005.[6]

Expanded Carrier Screening

ECS involves screening individuals or couples for disorders in many genes (up to 100s) by next-generation sequencing. ECS panels may screen for diseases that are present with increased frequency in specific populations but also include a wide range of diseases for which the patient is not at increased risk of being a carrier. Chokoshvili et al (2018) identified 16 providers offering ECS as of January 2017; the number of conditions tested ranged from 41 to 1792.[7] There was high variability in the genes covered by the different ECS panels with only three conditions (cystic fibrosis, maple syrup urine disease 1b, and Niemann-Pick disease) included in all 16 panels. For ECS panels in which the same disease was screened, there were notable differences in the specific mutations assessed and in variant interpretation and reporting strategies.

Arguments for ECS include the potential to assess ethnicity, identify more potential conditions, efficiency, and cost. Uncertain are the possible downsides of screening individuals at low-risk, including 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 conditions included in ECS panels are not standardized and the panels may 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 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 (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 and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services 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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38. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Article: Billing and Coding: Molecular Pathology Procedures (A56199), Revision Effective Date 10/03/2019.