

Corporate Medical Policy

Carrier Screening for Genetic Disease

File Name: carrier_screening_for_genetic_disease
Origination: 12/2013
Last Review: 4/2023

Description of Procedure or Service

This policy is largely based on general principles of carrier screening and accepted practice guidelines from major medical societies and provides a framework for evaluating these tests. Reported analytic validity (technical accuracy) of targeted carrier screening tests is high, but analytic validity of expanded carrier screening (ECS) panels is uncertain and requires careful evaluation. Clinical validity of carrier screening is difficult to assess because there is no criterion standard for carrier status. For clinical utility, the disorder(s) of interest should be clinically severe with a high frequency of carriers in the screened population. Additionally, access to genetic counseling is advised. ECS panels have significant limitations, including increased false positives and variants of uncertain significance due to multiple testing, and false negatives due to rare variants not included in panel testing. Based on these findings, carrier screening for genetic diseases is considered medically necessary when certain criteria are met (see Policy statements).

Carrier screening is testing 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 pre-conception periods. This policy offers a framework for evaluating the clinical utility of risk-based and expanded carrier screening (ECS). This policy applies only if there is not a separate Corporate Medical Policy that outlines specific criteria for carrier testing. If a separate policy does exist, then the criteria for medical necessity in that policy supersede the guidelines in this policy. See **related policies** listed at the end of this section.

Targeted Carrier Screening

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.

Expanded carrier screening (ECS)

New technologies have made it possible to screen for variants in many genes more efficiently than testing variants in a single gene or a small number of population-specific variants in several genes.

Expanded carrier screening involves screening individuals or couples for disorders in many genes (up to 100s) by next generation sequencing (NGS). 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. 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 (eg, due to variable expressivity and uncertain penetrance). The conditions included in ECS panels are not standardized and the panels

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may include many conditions not routinely evaluated and for which there are not existing professional guidelines.

Definitions

Carrier screening: Carrier genetic screening 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 variant 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 variant from both parents) manifest the disorder.

Compound heterozygous: The presence of two different variant 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 variant 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 variant not 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 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.

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.

Related Policies:

Cardiovascular Disease Risk Assessment AHS-G2050

Genetic Testing For Cystic Fibrosis AHS-M2017

Genetic Testing For Fanconi Anemia AHS-M2077

Prenatal Screening (Genetic) AHS-M2179

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

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Policy

BCBSNC will provide coverage for Carrier Testing for Genetic Disease when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Carrier Testing for Genetic Disease is covered

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*)

*First-degree relatives include biological parent, brother, sister, or child; second-degree relatives include a 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 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.

When Carrier Testing for Genetic Disease is not covered

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

Policy Guidelines

*If there is no family history of risk-based 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 and Genomics (ACMG) recommends testing for specific variants, 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 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 states that although commercial laboratories offer expanded carrier screening panels, there has been no professional guidance as to which disease genes and variants to include.

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The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 690 (reaffirmed in 2020) provides 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 1 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 of 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.”

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.

Individuals of Ashkenazi Jewish descent have cumulatively high carrier rates for multiple conditions, notably 1 in 4 and 1 in 5 when all disorders are considered. Recommendations for carrier screening for Ashkenazi Jewish individuals by ACOG and ACMG are summarized below.

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 1/3,000; carrier rate 1/30),
- Canavan disease (disease incidence 1/6,400; carrier rate 1/41), and
- Cystic fibrosis (disease incidence 1/2,500-3,000; carrier rate 1/24) and
- Familial dysautonomia (disease incidence 1/3,600; carrier rate 1/31) and
- Fanconi anemia (group C) (disease incidence 1/32,000; carrier rate 1/89), and
- Niemann-Pick (type A) (disease incidence 1/32,000; carrier rate 1/90), and
- Bloom syndrome (disease incidence 1/40,000; carrier rate 1/100), and
- Mucopolysaccharidosis IV (disease incidence 1/62,500; carrier rate 1/96), and
- Gaucher disease (disease incidence 1/900; carrier rate 1/15), and
- Familial hyperinsulinism (carrier rate 1/52), and
- Glycogen storage disease type I (carrier rate 1/71), and
- Joubert syndrome (carrier rate 1/92), and
- Maple syrup urine disease (carrier rate 1/81), and
- Usher syndrome (carrier rate \leq 1/40).

Table 2 provides the recommendations by indication for targeted risk-based screening based on the current ACOG and ACMG guidelines.

| Society | Recommendation | Year |
|--------------------------------|---|-------------|
| Cystic fibrosis | | |
| ACOG | Cystic fibrosis carrier screening should be offered to all women considering pregnancy or are pregnant. | 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. | 2013 |
| Spinal muscular atrophy | | |

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| 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 detection testing should be recommended for the low-risk partner. | 2017 |
| ACMG | Because spinal muscular atrophy is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity. | 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 | 2017 |
| Hemoglobinopathies (sickle cell disease, α- and β-thalassemia) | | |
| ACOG | A complete blood count with red blood cell indices should be performed in all women who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of a hemoglobinopathy. Ideally, this testing also should be offered to women before pregnancy. A hemoglobin electrophoresis should be offered to women before pregnancy. A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent). If red blood cell indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume, hemoglobin electrophoresis also should be performed. | 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. | 2017 |

The evidence for individuals who are asymptomatic but at risk for having an offspring with an inherited recessive genetic disorder who receive targeted-based carrier screening 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 avoidance of pregnancy, preimplantation genetic diagnosis, in vitro fertilization, invasive prenatal testing, and adoption. Therefore, the evidence is sufficient to determine the technology results in a meaningful improvement in the net health outcome.

The evidence for expanded carrier screening (ECS) in individuals who are either at increased risk or population risk for having an offspring with an inherited recessive genetic disorder, includes studies supporting clinical validity and clinical utility. Relevant outcomes are test validity, and changes in reproductive decision making. Studies have found that ECS identifies more carriers and potentially

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affected fetuses. However, evidence to support the clinical validity of expanding carrier screening beyond risk-based recommendations is limited and accompanied by some concerns including; interlaboratory inconsistency of variant pathogenicity assessment, the validity of disease severity classifications for rare disorders, and the uncertainty that the offspring will be affected by severe phenotype for all the disorders included in a panel. As well, many of the genes in ECS do not meet the ACOG consensus-driven criteria of at least 1% carrier rate for all ethnic groups. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81329, 81336, 81337, 81412, 81443

If CPT Tier 1 or Tier 2 molecular pathology codes are available for the specific test, they should be used. If the test has not been codified by CPT, the unlisted molecular pathology code 81479 would be used.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

ACOG Committee Opinion No. 442: Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. *Obstet Gynecol* 2009; 114(4):950-3.

Gross SJ, Pletcher BA, Monaghan KG. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med*. 2008 January; 10(1): 54–56.

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 Sep-Oct; 6(5): 387–391.

ACOG Publishes Guidelines on Hemoglobinopathies in Pregnancy. *Practice Guideline Briefs. Am Fam Physician*. 2007 Oct 15;76(8):1229-1230.

Grody WW, Thompson BH, Gregg AR et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med* 2013; 15(6):482-3.

https://www.acmg.net/docs/Prenatal_Preconception_Expanded_Carrier_Screening_Statement_GiM_June_2013.pdf

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.107, 11/14/13

Medical Director review 12/2013

Specialty Matched Consultant Advisory Panel review 8/2014

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ACOG Committee Opinion No. 690: Carrier screening in the age of genomic medicine. *Obstet Gynecol.* Mar 2017;129(3):e35-e40.

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Policy Implementation/Update Information

1/28/14 New policy developed. 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

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threshold considered appropriate for testing for a particular condition; 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. An association of the marker with the disorder has been established. Expanded carrier screening panels are considered to be not medically necessary. Medical Director review 12/2013. (mco)

- 9/9/14 Related Policies list updated. Specialty Matched Consultant Advisory Panel review 8/2014. No changes to Policy Statements. (mco)
- 11/11/14 Regulatory Section under Description section updated. Policy Guidelines section updated, including addition of “Spinal Muscular Atrophy” information and archived related policies removed. No changes to Policy Statements. (td)
- 7/1/15 Description section revised to list current active policies under Related Policies section. (td)
- 10/1/15 Specialty Matched Consultant Advisory Panel review 8/26/2015. Medical Director review 8/2015. Description section updated to remove archived related policies. Policy Statement remains unchanged. (td)
- 12/30/15 Description section updated. Billing/Coding section updated to include code 81412 effective 1/1/16. Policy Guidelines section updated. References updated. (td)
- 8/30/16 Specialty Matched Consultant Advisory Panel review 7/2016. Medical Director review 7/2016. (jd)
- 12/30/16 Updated Related Policies section along with minor revisions to policy guidelines section. No change to policy statement/intent. (jd)
- 5/26/17 Policy title changed from “Carrier **Testing** for Genetic Diseases” to “Carrier Screening for Genetic Diseases”. Description section and Policy Guidelines updated. Genetic nomenclature updated throughout policy, no change to policy intent. Updated Related Policies. References updated. Medical Director review 4/2017. (jd)
- 8/11/17 Minor update to Policy Guidelines. Specialty Matched Consultant Advisory Panel review 7/2017. Medical Director review 7/2017. (jd)
- 9/29/17 Minor revision to Description section. Major revision to Policy Guidelines to include current ACOG guidelines and added Table 2 providing recommendations for risk-based screening based on current ACOG and ACMG guidelines. No change to policy intent. References updated. (jd)
- 8/24/18 Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2018. (jd)
- 12/31/18 Added CPT codes 81329, 81336, 81337, and 81443 to Billing/Coding section for effective date 1/1/19. (jd)
- 4/1/19 Related Policies section updated. (jd)

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- 8/13/19 Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (jd)
- 7/28/20 Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)
- 9/7/21 Minor revisions. References updated. Specialty Matched Consultant Advisory Panel review 7/2021. Medical Director review 7/2021. (jd)
- 9/13/22 References updated. Specialty Matched Consultant Advisory Panel review 7/2022. Medical Director review 7/2022. No change to policy statement. (tm)
- 5/2/23 References, Description, Related Policies and Policy Guidelines updated. No change to policy statement. Specialty Matched Consultant Advisory Panel review 4/2023. Medical Director review 4/2023. (tm)

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