Carrier Screening for Genetic Disease

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 testing 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 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.

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 variants in many genes more efficiently than testing variants in a single gene or a small number of population-specific variants in several genes.

Commercial laboratories offer these expanded carrier screening panels (ECS), which is defined as a non-targeted approach to carrier screening. There is no standardization to the makeup of these
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genetic panels, the composition of the panels varies among labs, and different commercial products for the same condition may test a different sets of genes. Although ECS panels may include conditions that are routinely assessed in carrier screening, these ECS panels include many conditions that are not routinely evaluated and for which there are no 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 disease.

**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 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 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:**
- Assays of Genetic Expression to Determine Prognosis of Breast Cancer
- BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Therapy
- Cardiovascular Disease Risk Tests
- Circulating Tumor DNA for Cancer Management (Liquid Biopsy)
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DNA Based Testing for Adolescent Idiopathic Scoliosis
Molecular Analysis for Targeted Therapy for Non-Small Cell Lung Cancer (NSCLC)
Fetal RHD Genotyping Using Cell-Free Fetal DNA
Gene Expression Testing in the Evaluation of Patients With Stable Ischemic Heart Disease
Genetic and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer
General Approach to Evaluating the Utility of Genetic Panels
General Approach to Genetic Testing
Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
Genetic Testing for Alpha-1 Antitrypsin Deficiency
Genetic Testing for Alpha Thalassemia
Genetic Testing for Alzheimer’s Disease
Genetic Testing for Breast and Ovarian Cancer
Genetic Testing for CADASIL Syndrome
Genetic Testing for Cardiac Ion Channelopathies
Genetic Testing for Colon Cancer
Genetic Testing for Cutaneous Malignant Melanoma
Genetic Testing for Dilated Cardiomyopathy
Genetic Testing for Duchenne and Becker Muscular Dystrophy
Genetic Testing for Epilepsy
Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder
Genetic Testing for FMR1 Mutations Including Fragile X Syndrome
Genetic Testing for Hereditary Hearing Loss
Genetic Testing for Hereditary Hemochromatosis
Genetic Testing for Hereditary Pancreatitis
Genetic Testing for Heterozygous Familial Hypercholesterolemia
Genetic Testing for Lactase Insufficiency
Genetic Testing for Macular Degeneration
Genetic Testing for Myeloproliferative Neoplasms
Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy
Genetic Testing for PTEN Hamartoma Tumor Syndrome
Genetic Testing for Rett Syndrome
Genetic Testing for Statin-induced Myopathy
Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathy
Laboratory and Genetic Testing for use of 5-Fluorouracil (5-FU) in Patients with Cancer
Laboratory Tests For Heart Transplant Rejection
Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification
Microarray-based Gene Expression Testing for Cancers of Unknown Primary
Moderate Penetration Variants Associated with Breast Cancer in Individuals at High Risk
Molecular Markers in Fine Needle Aspirates of the Thyroid
Multigene Expression Assay for Predicting Recurrence in Colon Cancer
Noninvasive Prenatal Testing for Fetal aneuploidies Using Cell-Free Fetal DNA
PathFinderTG® Molecular Testing
Proteomics-based Testing for Related to Ovarian Cancer
Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers
Serum Biomarker Human Epididymis Protein 4 (HE4)
Urinary Tumors Markers for Bladder Cancer
Use of Common Genetic Variants to Predict Risk of Non-familial Breast Cancer
Vectra® DA Blood Test for Rheumatoid Arthritis
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

***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.

Policy
Carrier Screening for Genetic Disease

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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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.

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.

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 1/3,000; 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), 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. 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 genetic counseling, if both parents are determined to be carriers.

Cystic Fibrosis
Cystic fibrosis (CF) is the most common life-threatening autosomal recessive condition in the non-Hispanic white population. Carrier rates are 1 in 24 in the Ashkenazi Jewish population and 1 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 all individuals 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 and reaffirmed in 2013, use a 23-variant panel and were developed after assessing the initial experiences on implementation of CF 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.

Spinal Muscular Atrophy
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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. 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, 3 phenotypes are observed: In type 1 SMA (Werdnig-Hoffmann), severe, generalized muscle weakness and hypotonia are present at birth or within 3 months, and death from respiratory failure usually occurs before age 2 years. In type 2 SMA, children can sit, although they are unable to stand or walk unaided; survival is typically beyond age 4 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.

Recommendations from ACMG and ACOG for SMA carrier screening differ. ACMG’s 2008 guideline, reaffirmed in 2013, recommends carrier testing for SMA in all couples regardless of race or ethnicity. ACOG’s 2017 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 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.

The evidence for carrier screening in individuals who are asymptomatic but at risk for having an offspring with inherited single-gene disorders who receive risk-based carrier screening 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 genetic testing can be used to assist individuals with 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for expanded carrier screening (ECS) in individuals who are asymptomatic but at risk for having an offspring with inherited single-gene disorders includes studies on analytic validity, clinical validity, and indirectly clinical utility. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. Analytic validity of expanded carrier screening panels will depend on the molecular method used; two identified studies support the analytic validity for ECS, but variant ascertainment with NGS requires careful evaluation. Three studies have found that ECS identifies more carriers and potentially 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 agreement of variant pathogenicity assessment when sequencing identified rare variants, the validity of disease severity classifications for rare disorders, and the certainty of predicted risk that the offspring will be affected by severe phenotype for all the disorders included in a panel. 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:81412
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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


Medical Director review 12/2013
Specialty Matched Consultant Advisory Panel review 8/2014


Specialty Matched Consultant Advisory Panel review 8/2015
Medical Director review 8/2015


Medical Director review 7/2016

For policy titled: Carrier Screening for Genetic Disease


Medical Director review 4/2017
Specialty Matched Consultant Advisory Panel review 7/2017
Medical Director review 7/2017
Carrier Screening for Genetic Disease

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 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)


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)


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)


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purposes only and is based on research of current medical literature and review of common medical practices in the treatment
and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review
and revise its medical policies periodically.