Carrier Testing for Genetic Diseases

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Section: Medical

Place(s) of Service: Outpatient

Precertification is required for this service.

I. 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 concept review offers a framework for evaluating the utility of carrier genetic testing.

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 action ability of information obtained. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.
II. Policy

A. Carrier testing for genetic diseases is covered when one of the following criteria is met:
   1. The individuals have a previously affected child with the genetic disease OR
   2. One or both individuals have a first- or second-degree relative who is affected OR
   3. One or both individuals have a first-degree relative with an affected offspring OR
   4. One individual is known to be a carrier OR
   5. 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 Section III.A)

B. AND all of the following criteria are met:
   1. 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.
   2. 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.
   3. The genetic test has adequate clinical validity to guide clinical decision making and residual risk is understood (see Policy Guidelines Section III.B).
   4. An association of the marker with the disorder has been established.

C. Expanded carrier screening panels are not covered (see Policy Guidelines Section III.C.)

III. Policy Guidelines

A. If there is no family history of 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 mutations, which will result in carrier detection rate of 95% or higher for most disorders.

C. 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 (eg, ethnic-specific screening or pan-ethnic testing for cystic fibrosis). An ACMG position statement notes that although commercial laboratories offer expanded carrier screening panels, there has been no professional guidance as to which disease genes and mutations to include.

D. 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.

E. Carrier testing should only be performed in adults.

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

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

1. Tay-Sachs disease (disease incidence 1/3000; carrier frequency 1/30), and
2. Canavan disease (1/6400; 1/40), and
3. cystic fibrosis (1/2500-3000; 1/29), and
4. familial dysautonomia (1/3600; 1/32).

In addition, ACMG recommends the following also offered to all individuals of Ashkenazi Jewish descent who are pregnant or considering pregnancy:

1. Fanconi anemia (group C) (1/32,000; 1/89), and
2. Niemann-Pick (type A) (1/32,000; 1/90), and
3. Bloom syndrome (1/40,000; 1/100), and
4. mucolipidosis IV (1/62,500; 1/127), and
5. 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 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 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 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 ACMG in 2004 (Watson et al, 2004) and reaffirmed in 2013 use a 23-mutation panel and were developed after assessing the initial experiences on 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 motoneurons 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 (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 posttest education and counseling for SMA screening.

For details, see Practice Guidelines and Position Statements section.

Coding

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.

Effective in 2016, this is a specific CPT code for a genomic sequencing panel for Ashkenazi Jewish associated disorders:

81412 Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1.

IV. Administrative Guidelines

A. Precertification is required for carrier testing for genetic diseases. To precertify, please complete HMSA’s Precertification Request and mail or fax the form as indicated along with the required documentation.

B. Applicable codes are as follows:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>V26.31</td>
<td>Testing of female genetic disease carrier status</td>
</tr>
<tr>
<td>V26.34</td>
<td>Testing of male for genetic disease carrier status</td>
</tr>
<tr>
<td>V83.01-V83.02</td>
<td>Hemophilia A carrier</td>
</tr>
<tr>
<td>V83.81, V83.89</td>
<td>Other genetic carrier status (includes cystic fibrosis)</td>
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</tbody>
</table>
**ICD-10-PCS Codes** | **Description**
--- | ---
| | Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.

**ICD-9-CM - Codes** | **Description**
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| | Diagnosis coding would depend on the condition for which the testing is being performed, if the test is being performed as screening or carrier testing, and any family history of the condition.

V. **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 evidence review applies only if there is no separate Medical Policy Reference Manual (MPRM) evidence review that outlines specific criteria for carrier testing. If a separate MPRM evidence review exists, then criteria for medical necessity in that evidence review 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 1 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 1 normal and 1 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 2 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 (eg, if the individual has a disease-causing mutation that wasn’t included in the test assay).

VI. Rationale

This evidence review was created in October 2013 and has been updated with literature review through August 31, 2015 (see Appendix Table 1 for genetic testing categories).

**General Principles of Carrier Screening for Genetic Diseases**

This evidence review is largely based on 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, or performed in a Clinical Laboratory Improvement Amendment–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 3 main principles: (1) analytic validity (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 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
Analytic validity of many of the targeted carrier screening tests has been reported to be high. For example, 1 major laboratory has reported that the analytic validity of its cystic fibrosis (CF) 32-mutation panel and their Ashkenazi Jewish panel (which includes testing for 8 conditions, as recommended by the American College of Medical Genetics [ACMG], plus CF) is 99%. For expanded carrier screening panels, analytic validity is either unknown (no published data) or cannot be adequately assessed due to weaknesses in assay validation.

Clinical Validity
Clinical validity of carrier screening is difficult to assess because there is no criterion standard for carrier status that can be used for 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
Clinical utility of carrier testing is defined by how 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 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, current limitations of these expanded panels include technical and interpretive limitations and ethical and genetic counseling challenges, as outlined next.

In 2015, a joint statement on ECS was issued by ACMG, American College of Obstetricians and Gynecologists, the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine. The statement was not meant to replace current screening guidelines but to demonstrate an approach for health care providers and laboratories
who are seeking to or are currently offering ECS panels. Some of the points considered include the following.

- ECS panels include most of the conditions recommended in current guidelines; however, molecular methods used in ECS are not as accurate as methods recommended in current guidelines for: hemoglobinopathies, which require use of mean corpuscular volume and hemoglobin electrophoresis, or for Tay-Sachs disease. The detection rate for Tay-Sachs carrier status is low in non-Ashkenazi populations using molecular testing for the 3 common Ashkenazi mutations - currently, hexoaminidase A enzyme analysis on blood is the best method to identify carriers in all ethnicities.

- “Patients should be aware that newborn screening is mandated by all states and can identify some genetic conditions in the newborn. However, newborn screening may include a different panel of conditions than ECS. Newborn screening does not usually detect children who are carriers for the conditions being screened so will not necessarily identify carrier parents at increased risk.”

- ECS can be performed by genotyping, which searches for known pathogenic and likely pathogenic variants, or by DNA sequencing, which analyzes the entire coding region of the gene and identifies alterations from the normal sequence. Genotyping includes selected variants, but sequencing has the potential to identify benign and likely benign variants and variants of unknown significance, in addition to pathogenic variants. Therefore, ECS panels should only include genes and variants with a well-understood relationship with a phenotype. When carrier frequency and detection rate are both known, residual risk estimation should be provided in the lab report.

- Conditions with unclear value on preconception and prenatal screening panels include α1-antitrypsin (A1AT), methylene tetrahydrofolate reductase (MTHFR), and hereditary hemochromatosis (HH).

There is currently little evidence that addresses reproductive outcomes using ECS. Future research needs in ECS should focus on data collection and development of a curated data repository, and education of health care providers and patients. To improve the predictive value of ECS, previously unreported and relatively rare variants and full phenotypes of homozygous and compound heterozygotes should be collected and made available. Determining the frequency of variants in previously untested ethnic and racial groups is required because risks associated with gene variants may vary with different genetic backgrounds and in different environmental situations. Collaborative analysis among laboratories is necessary to further understanding of ECS.

A 2011 study by Bell et al described the development of an ECS panel for 448 severe recessive diseases of childhood, using next-generation sequencing (NGS). The authors tested 104 unrelated DNA samples. They noted that although technical standards and guidelines for laboratory-developed genetic testing for rare disorders in accredited laboratories have been established, there are several challenges in their adoption for NGS and for bioinformatic-based testing of many conditions. Specific national standards for quality assurance, quality control, test accessioning and reporting, and proficiency evaluation do not currently exist. Also, issues of specificity and false
positives are complex when hundreds of genes are being sequenced simultaneously and need to be addressed.

Lazarin et al (2013) reported on carrier status from an ethnically diverse clinical sample of 23,452 individuals. Using the Counsyl test screening platform, they assayed 417 disease-causing mutations associated with 108 recessive diseases. Of the individuals tested, 5633 (24%) were heterozygous for at least 1 condition, and 5.2% were identified as carriers for multiple disorders. Of 127 carrier couples identified (ie, pairs of individuals identified as partners by self-report who were both found to share heterozygosity for at least 1 disease), 47 (37%) were for α1-antitrypsin deficiency, a condition that has reduced penetrance, variable severity, and uncertain clinical presentation in the newborn period and into adulthood. The American Thoracic Society and European Respiratory Society discourage genetic testing for α1-antitrypsin deficiency in asymptomatic adults with no increased risk for this disease.

In March 2011, 6 U.S. academic centers convened focus groups to examine genetics professionals’ views on ECS. Forty genetics professionals, including those specializing in medical genetics, pediatric genetics, genetic counseling, public health genetics, primary care, laboratory medicine, and law and bioethics, aimed to clarify how genetics professionals view potential benefits and challenges of ECS. Overall, participants agreed that there was financial value in ECS panels compared with conventional carrier screening. However, their findings highlighted major limitations of ECS. Concerns included the following:

- Use of ECS panels would be a significant departure from clinical practice guidelines in genetic and reproductive health care in the United States, and carrier screening guidelines currently exist for only a few of the genetic disorders evaluated by ECS panels.
- Technical limitations of ECS include the inability to fully rule out the possibility of severe recessive diseases due to rare mutations that could be identified by alternative methods such as DNA sequencing, and, there are gaps in coverage of both specific genes and individual mutations included in the ECS panels.
- Current ECS panels typically examine only a fraction of the many genes associated with genetic disorders and limit their evaluation to common genetic mutations within those genes.
- Reproductive health care providers might fail to recommend more conventional forms of targeted genetic evaluation, such as screening tests indicated by a couple’s ethnicity, based on erroneous perceptions about the coverage of ECS products being marketed as universal in scope. Less common mutations in specific ethnic populations may not be included, and couples may be falsely reassured by “negative” results.
- As the number of individual assays on a multiplexed genetic test increases, the likelihood of erroneous results (eg, false positives) and clinically ambiguous findings (eg, variants of unknown significance) increases significantly.
• As carrier screening panels expand to include less common genetic diseases, interpretation of mutation results is hindered by lack of data on clinical phenotypes associated with rare variants.

In 2013, Wienke et al commented on the limitations of using ECS panels. The authors stated that:

• Patients may not understand the nature of every disease on the panel, confounding the process of informed consent.

• In practice, it is infeasible to inform patients of the nature of each condition tested, and many health care providers are unfamiliar with some of the conditions tested, making it difficult to communicate residual risk and action ability of information obtained.

• Panels usually include diseases with decreased penetrance and variable expressivity that are unlikely to be life-threatening in a patient with a negative family history (eg, factor V Leiden thrombophilia, hemochromatosis, methylenetetrahydrofolate reductase [MTHFR] deficiency).

• Screening for mutations that have unclear clinical significance has unclear implications in reproductive decision making.

• It is possible that a test primarily designed to assess reproductive risk will inadvertently identify an asymptomatic individual with the disease, which poses many challenges. These include unanticipated psychosocial burden to patients, and a burden to the health care system in general as a person identified through this method may undergo additional baseline testing for the disease and receive follow-up for the disease that may otherwise have been unnecessary.

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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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<th>Trial Name</th>
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<td>Clinical Implementation of Carrier Status Using Next Generation S</td>
<td>400</td>
<td>May 2017</td>
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<td>NCT01902901</td>
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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.

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Practice Guidelines and Position Statements

Ethnic Groups with a Higher Carrier Rate for a Particular Condition

Ashkenazi Jewish Population

In 2014, the American Congress of Obstetricians and Gynecologists (ACOG) reaffirmed a 2009 committee opinion that carrier screening for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia should be offered to Ashkenazi Jewish individuals before conception or during pregnancy so that a couple has an opportunity to consider prenatal diagnostic testing options. The committee opinion stated that individuals of Ashkenazi Jewish descent may inquire about the availability of carrier screening for other disorders found among individuals of Eastern European Jewish descent, and that carrier screening is available for mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease, and that patient education materials can be made available so that interested patients can make informed decisions about having additional screening tests. When only 1 partner is of Ashkenazi Jewish descent, that individual should be screened first. If that individual is a carrier, the other partner should be offered screening; however, the couple should be informed that because carrier frequency and detection rate in non-Jewish individuals is unknown for all of these disorders (except for Tay-Sachs disease and cystic fibrosis [CF]), it is difficult to predict the couple’s risk of having a child with one of the disorders. If an individual has a positive family history for one of these disorders, he or she should be offered carrier screening for that specific disorder. When both partners are carriers of one of these disorders, they should be referred for genetic counseling and offered prenatal diagnosis.
In 2013, the American College of Medical Genetics and Genomics (ACMG) reaffirmed a 2008 guideline that recommended carrier screening for CF, Canavan disease, familial dysautonomia, and Tay-Sachs disease be offered to all individuals of Ashkenazi Jewish descent who are pregnant, or considering pregnancy. ACMG also recommended that carrier screening be offered for Fanconi anemia (group C), Niemann-Pick (type A), Bloom syndrome, mucolipidosis IV, and Gaucher disease.

According to ACMG, if only 1 member of the couple is Jewish, ideally, that individual should be tested first. If the Jewish partner has a positive carrier test result, the other partner (regardless of ethnic background) should be screened for that particular disorder. One Jewish grandparent is sufficient to offer testing.

**Hemoglobinopathies**
In 2013, ACOG reaffirmed a 2007 guideline for hemoglobinopathies in pregnancy, which included recommendations for carrier screening. For carrier screening, individuals of African, Southeast Asian, and Mediterranean descent are at risk for being carriers of hemoglobinopathies; ACOG recommended that individuals from these ethnic groups be offered carrier screening and, if both parents are determined to be carriers, genetic counseling. A complete blood count and hemoglobin electrophoresis are appropriate laboratory tests for screening for hemoglobinopathies.

**Cystic Fibrosis**
The initial ACMG Cystic Fibrosis Carrier Screening Working Group recommended that laboratories use a pan-ethnic panel of 25 mutations present in at least 0.1% of patients with classic CF.12 Current guidelines, revised by ACMG in 200413 and reaffirmed in 2013, recommend a 23-mutation panel and were developed after assessing initial experiences on implementation of CF screening into clinical practice. CF screening also may identify 5T/7T/9T variants in the CFTR gene, which vary between individuals. Genetic counseling is important to discern whether the combination of mutations and variants would cause classic or atypical CF.

Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening because it may yield results difficult to interpret. This type of testing is generally reserved for patients with CF, patients with a family history of CF, males with congenital bilateral absence of the vas deferens, or newborns with a positive newborn screening result when mutation testing, using the standard 23-mutation panel, has a negative result. Because carrier screening detects most mutations, sequence analysis should be considered only after discussion with a genetics professional to determine if sequencing will be informative after standard screening has been performed.

In 2011, ACOG issued an update on carrier screening for CF, and the Committee on Genetics provided the following guidelines:

- It is important that CF screening continue to be offered to women of reproductive age. It is becoming increasingly difficult to assign a single ethnicity to individuals. It is reasonable, therefore, to offer CF carrier screening to all patients. Screening is most efficacious in the non- Hispanic white and Ashkenazi Jewish populations.

- It is prudent to determine whether the patient has been previously screened before ordering CF screening that may be redundant. If a patient has been screened previously, CF screening results should be documented, but the test should not be repeated.
• Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening.

• Newborn screening panels that include CF screening do not replace maternal carrier screening.

• If a woman with CF wants to become pregnant, a multidisciplinary team should be consulted to manage issues regarding pulmonary function, weight gain, infections, and increased risks of diabetes and preterm delivery.

• For couples in which both partners are carriers, genetic counseling is recommended to review prenatal testing and reproductive options.

• For couples in which both partners are unaffected but one or both has a family history of CF, genetic counseling and medical record review should be performed to identify whether CFTR mutation analysis in the affected family member is available.

• If a woman’s reproductive partner has CF or apparently isolated congenital bilateral absence of the vas deferens, the couple should be referred to a genetics professional for mutation analysis and consultation.

**Spinal Muscular Atrophy**

Current practice guidelines for spinal muscular atrophy (SMA) carrier testing from ACMG and ACOG conflict. 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 limits SMA carrier screening (1) to those with a family history of SMA or SMA-like disease, and (2) to those who request SMA carrier screening and have completed genetic counseling to review sensitivity, specificity, and limitations of screening. The genetics of SMA is complex, involving 2 genes; 95% of patients have a deletion in SMN1, but variable copy number of SMN2 affects phenotypic expression (greater copy number is associated with milder disease). Further, copy number of SMN1 can vary, confounding interpretation of a negative (normal) result (eg, 2 SMN1 copies on 1 chromosome may mask SMN1 deletion from the other chromosome). Because of this complexity and residual risk with a negative result, ACOG opinion authors recommended pilot studies to determine best practices for pre- and posttest education and counseling before implementing pan-ethnic SMA carrier screening.

**Expanded Panel Testing**

In 2013, ACMG issued a position statement on prenatal/preconception expanded carrier testing. For a particular disorder to be included in carrier screening, the following criteria should be met:

1. Disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction.

• The inclusion of disorders characterized by variable expressivity or incomplete penetrance and those known to be associated with a mild phenotype should be optional and made transparent when using these technologies for screening. This recommendation is guided by the ethical principle of nonmaleficence.
2. When adult-onset disorders (disorders that could affect offspring of the individual undergoing carrier screening once offspring reach adult life) are included in screening panels, patients must provide consent to screening for these conditions, especially when there may be implications for the health of the individual being screened or for other family members.

- This recommendation follows the ethical principles of autonomy and nonmaleficence.

3. For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed.

- Laboratories should specify in their marketing literature and test results how residual risk was calculated using pan-ethnic population data or a specific race/ethnic group.
- The calculation of residual risk requires knowledge of 2 factors: one is the carrier frequency within a population, the other is the proportion of disease-causing alleles detected using the specific testing platform. Laboratories using multiplex platforms often have limited knowledge of one or both factors. Laboratories offering expanded carrier screening should keep data prospectively and regularly report findings that allow computation of residual risk estimates for all disorders being offered. When data are inadequate, patient materials must stress that negative results should not be overinterpreted.

4. There must be validated clinical association between the mutation(s) detected and the severity of the disorder.

- Patient and provider materials must include specific citations that support inclusion of the mutations for which screening is being performed.

5. ECS tests must comply with ACMG’s Standards and Guidelines for Clinical Genetics Laboratories, including quality control and proficiency testing.

- Quality control should include the entire test process, including preanalytical, analytical, and postanalytical phases. Test performance characteristics should be available to patients and providers accessing testing. A highly multiplexed approach will require a more generic consent process than is typically used for single-disease screening because it may be impractical for a clinician to discuss each disease included in a multidisease carrier screening panel. An appropriately tailored informational pamphlet or web site, containing a brief description of each disorder included in a test panel, should be available to patients undergoing or considering an expanded prenatal/preconception carrier screening panel. Genetic counseling before testing should be available to those who desire this, and posttest genetic counseling for those with positive screening results is recommended.
U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force makes recommendations for carrier testing for BRCA-associated genetic diseases and for hereditary hemochromatosis, topics that are not included in this evidence review but in separately for each condition.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References