**Policy Statement**

Carrier screening (related to pregnancy or planned pregnancy) for genetic diseases in biological parents may be considered **medically necessary** when **one or more** of the following criteria is met:

- One or both individuals have a first- or second-degree relative who is affected (see Policy Guidelines section*)
- One individual is known to be a carrier
- 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 1 section)

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 2 section)
- 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**.

Limited genetic panels (i.e., code 81443, see Coding in the Policy Guidelines section) that include testing for Spinal Muscular Atrophy (SMN1 gene) and Cystic Fibrosis (CFTR gene) may be considered **medically necessary** as an alternative to testing of individual genes for all women who are pregnant or are considering pregnancy.

Expanded carrier screening panels (other than code 81443) are considered **investigational** (see Policy Guidelines 3 section). Some larger panels can be approved if the request is only for CPT 81443.

**Note:** Screening for Cystic Fibrosis (CFTR) and Spinal Muscular Atrophy (SMN1) are recommended for all women who are pregnant or considering pregnancy (see Policy Guidelines). CFTR is part of the 81443 panel, but SMN1 should also be included in any panel requested using 81443.

**Note:** Screening for Tay-Sachs disease (HEXA) and Fragile X syndrome (FMR1) are based on the risk from the family history (see Policy Guidelines). HEXA is part of the 81443 panel, but FMR1 is specifically excluded from the 81443 panel (by CPT guidelines) and may need to be tested separately when indicated (CPT 81243).

**Note:** 8 of the 9 genes in the panel 81412 for Ashkenazi Jewish associated disorders are included in the panel 81443, but 81412 does not include CFTR, SMN1 or other genes of use for a carrier panel and should not be used instead of 81443 for carrier screening.
Policy Guidelines

*Note: First-degree relatives include biological parent, brother, sister, or child; second-degree relatives include biologic grandparent, aunt, uncle, niece, nephew, grandchildren, and half-sibling.

Policy Guidelines 1
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.

Policy Guidelines 2
The American College of Medical Genetics and Genomics (ACMG) has recommended testing for specific variants, which will result in carrier detection rate of 95% or higher for most disorders.

Policy Guidelines 3
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 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 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.

Genetics Nomenclature Update
Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—‘‘pathogenic,’’ ‘‘likely pathogenic,’’ ‘‘uncertain significance,’’ ‘‘likely benign,’’ and ‘‘benign’’—to describe variants identified that cause Mendelian disorders.
### Targeted Risk-Based Screening Recommendations

ACOG and ACMG have issued numerous guidelines on targeted risk-based screening (see Table PG1).

**Table PG1. ACOG and ACMG Recommendations for Risk-Based Screening**

<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendation</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cystic fibrosis</strong> (CTFR)</td>
<td>“Cystic fibrosis carrier screening should be offered to all women considering pregnancy or are pregnant.”</td>
<td>2017</td>
</tr>
<tr>
<td>ACOG</td>
<td>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.</td>
<td>2013</td>
</tr>
<tr>
<td>ACMG</td>
<td>“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.”</td>
<td>2017</td>
</tr>
<tr>
<td>Spinal muscular atrophy (SMN1)</td>
<td>Because spinal muscular atrophy is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity.</td>
<td>2013</td>
</tr>
<tr>
<td>ACOG</td>
<td>“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.”</td>
<td>2017</td>
</tr>
<tr>
<td>ACMG</td>
<td>“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”</td>
<td>2017</td>
</tr>
</tbody>
</table>
Carrier Screening for Genetic Diseases

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.\(^a\)

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.

Gene names provided by the following:

ACOG\(^b\) and ACMG\(^a\) provided recommendations specific to individuals of Ashkenazi Jewish descent due to high carrier rates for multiple conditions in this population (see Table PG2). 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.

### Table PG2. ACMG (2008, 2013) and ACOG (2017) Carrier Screening Recommendations for Individuals of Ashkenazi Jewish Descent\(^a, b\)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sachs disease (HEXA)</td>
<td>1/3000</td>
<td>1/30</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Canavan disease (ASPA)</td>
<td>1/6400</td>
<td>1/40</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Cystic fibrosis (CTFR)</td>
<td>1/2500-3000</td>
<td>1/29</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Familial dysautonomia (ELP1)</td>
<td>1/3600</td>
<td>1/32</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Fanconi anemia (group C) (FANCC)</td>
<td>1/32,000</td>
<td>1/89</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Niemann-Pick disease type A (SMPD1)</td>
<td>1/32,000</td>
<td>1/90</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Bloom syndrome (BLM)</td>
<td>1/40,000</td>
<td>1/100</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Mucolipidosis IV (MCOLN1)</td>
<td>1/62,500</td>
<td>1/127</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Gaucher disease (GBA)</td>
<td>1/900</td>
<td>1/15</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Familial hyperinsulinism (ABC, KCN 11)</td>
<td>1/52</td>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Glycogen storage disease type I (G6PC, SLC37A4)</td>
<td>1/71</td>
<td></td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
### Table PG3. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>
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.

Coding

Effective January 1, 2019, a new CPT code describes genetic testing for severe inherited conditions:

- **81443**: Genetic testing for severe inherited conditions (e.g., cystic fibrosis, Ashkenazi Jewish-associated disorders [e.g., Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (e.g., ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)

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 following code would be used:

- **81479**: Unlisted molecular pathology procedure

The following is a specific CPT code for a genomic sequencing panel for Ashkenazi Jewish-associated disorders:

- **81412**: Ashkenazi Jewish-associated disorders (e.g., 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

### Table PG4. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

Carrier screening is performed to identify individuals at risk of having offspring with inherited single-gene disorders. Carriers are usually not at risk of developing the disease, but can pass pathogenic variants to their offspring. Carrier testing may be performed in the prenatal or preconception periods.

### Related Policies

- N/A
Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

A number of commercially available genetic tests exist for carrier screening. They range from testing for individual diseases, to small panels designed to address testing based on ethnicity as recommended by practice guidelines (American College of Obstetricians and Gynecologists, American College of Medical Genetics and Genomics), to large expanded panels that test for numerous diseases.

Rationale

Background

Inherited Recessive Disorders

There are more than 1300 inherited recessive disorders (autosomal or X-linked) that affect 30 out of every 10,000 children. 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.” Risk-based carrier screening 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 United States and Canada. An example of pan-ethnic screening involves cystic fibrosis, when the American College of Obstetricians and Gynecologists (ACOG) noted that ethnic intermarriage was increasing in the US and recommended pan-ethnic cystic fibrosis carrier screening in 2005.

Expanded Carrier Screening

Expanded carrier screening (ECS) 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. Chokoshvili et al (2018)
identified 16 providers offering ECS as of January 2017; the number of conditions tested ranged from 41 to 1792 (see Table 1). 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.

Table 1. Available Expanded Carrier Screening Tests as of January 2017.

<table>
<thead>
<tr>
<th>ECS</th>
<th>Provider</th>
<th>Country</th>
<th>No. Conditions Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>23andMe</td>
<td>23andMe</td>
<td>US</td>
<td>41</td>
</tr>
<tr>
<td>Baby Genes</td>
<td>Baby Genes Inc</td>
<td>US</td>
<td>71</td>
</tr>
<tr>
<td>Baylor Miraca Genetics</td>
<td>Baylor Genetics</td>
<td>US</td>
<td>158</td>
</tr>
<tr>
<td>Counsyl</td>
<td>Myriad Genetics</td>
<td>US</td>
<td>113</td>
</tr>
<tr>
<td>EGL Genetics</td>
<td>EGL Genetics LLC</td>
<td>US</td>
<td>147</td>
</tr>
<tr>
<td>GenPath Diagnostics</td>
<td>Gen Path</td>
<td>US</td>
<td>166</td>
</tr>
<tr>
<td>Good Start Genetics</td>
<td>Good Start Genetics</td>
<td>US</td>
<td>252</td>
</tr>
<tr>
<td>Igenomix</td>
<td>Igenomix</td>
<td>Spain</td>
<td>633</td>
</tr>
<tr>
<td>Integrated Genetics</td>
<td>LabCorp</td>
<td>US</td>
<td>135</td>
</tr>
<tr>
<td>Macrogen</td>
<td>Macrogen Inc</td>
<td>South Korea</td>
<td>1792</td>
</tr>
<tr>
<td>Natera</td>
<td>Natera Inc</td>
<td>US</td>
<td>272</td>
</tr>
<tr>
<td>NextStep Carrier Screening</td>
<td>Mount Sinai Hospital</td>
<td>US</td>
<td>256</td>
</tr>
<tr>
<td>Pathway Genomics</td>
<td>Pathway Genomics</td>
<td>US</td>
<td>73</td>
</tr>
<tr>
<td>Progenity</td>
<td>Progenity Inc</td>
<td>US</td>
<td>230</td>
</tr>
<tr>
<td>Recombine</td>
<td>CooperGenomics</td>
<td>US</td>
<td>314</td>
</tr>
<tr>
<td>Academic Medical Center Amsterdam</td>
<td></td>
<td>Netherlands</td>
<td>50</td>
</tr>
</tbody>
</table>

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 a potential for incorrect variant ascertainment and the consequences of screening for rare single-gene disorders in which the likely phenotype may be uncertain (e.g., due to variable expressivity and uncertain penetrance). The conditions included in ECS panels is not standardized and the panels may include many conditions not routinely evaluated and for which there are no existing professional guidelines.

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

Literature Review

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.
Targeted Risk-based Carrier Screening
Clinical Context and Test Purpose
The purpose of targeted risk-based carrier screening is to identify asymptomatic individuals who are heterozygous for serious or lethal single-gene disorders with the purpose of determining the risk of conceiving an affected child and inform reproductive decisions.

The question addressed in this evidence review is: Does the use of targeted risk-based carrier screening improve the net health outcome of asymptomatic individuals at risk of having offspring with inherited gene disorders?

The following PICOTS were used to inform literature selection.

Patients
The relevant population of interest are individuals or couples at risk for having offspring with inherited gene disorders due to family history, ethnicity, or race.

Interventions
The intervention of interest is targeted risk-based carrier screening with genes or focused gene panels specific to risk, for example, a Jewish Ashkenazi panel.

Comparators
The comparator of interest is no carrier screening.

Outcomes
The primary outcome of interest is reproductive decision making.

A beneficial outcome of a true test result is an informed reproductive decision that is consistent with prospective parent(s)' personal preferences and values. Informed reproductive decisions can include those concerning preimplantation genetic diagnosis, in vitro fertilization, not having a child, invasive prenatal testing, adoption, or pregnancy termination.

A harmful outcome is a reproductive decision based on an incorrect test or assessment of genotype-phenotype relationship. A false-positive result or incorrect genotype-phenotype association could lead to avoiding or terminating a pregnancy unnecessarily. A false negative test could lead to an affected offspring.

Timing
Preconception or prenatal periods.

Setting
Carrier screening is performed on DNA which can be sampled (e.g., from blood or saliva) in primary care, specialists offices or in tertiary care centers. Counseling should be performed by providers who are knowledgeable in genetics.

Study Selection Criteria
For the evaluation of the clinical utility of targeted risk-based carrier screening for genetic disorders, studies would need to use the test to inform reproductive decisions in asymptomatic individuals who are at risk of having an offspring with inherited recessive single-gene disorders. In addition, because the ACOG and the American College of Medical Genetics and Genomics (ACMG) consider risk-based carrier screening an established practice, guideline recommendations from these organizations will also be included in the evidence discussion.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires 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.

** Clinically Valid**  
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. 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%). 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.

**Targeted Risk-Based Screening Recommendations**  
ACOG and ACMG have issued numerous guidelines on targeted risk-based screening (see Table 2).

<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendation</th>
<th>Year</th>
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<tbody>
<tr>
<td>Cystic fibrosis*</td>
<td>&quot;Cystic fibrosis carrier screening should be offered to all women considering pregnancy or are pregnant.&quot;&lt;sup&gt;9&lt;/sup&gt;</td>
<td>2017</td>
</tr>
<tr>
<td>ACOG</td>
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<td>2013</td>
</tr>
<tr>
<td>ACMG</td>
<td>&quot;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.&quot;&lt;sup&gt;9&lt;/sup&gt;</td>
<td>2017</td>
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</table>
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.

ACOG9, and ACMG12, provided recommendations specific to individuals of Ashkenazi Jewish descent due to high carrier rates for multiple conditions in this population (see Table 3). 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.

Table 3. ACMG (2008, 2013) and ACOG (2017) Carrier Screening Recommendations for Individuals of Ashkenazi Jewish Descent9, 12

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sachs disease</td>
<td>1/3000</td>
<td>1/30</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>1/6400</td>
<td>1/40</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1/2500-3000</td>
<td>1/29</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Familial dysautonomia</td>
<td>1/3600</td>
<td>1/32</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Fanconi anemia (group C)</td>
<td>1/32,000</td>
<td>1/89</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Niemann-Pick disease type A</td>
<td>1/32,000</td>
<td>1/90</td>
<td>R</td>
<td>C</td>
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<tr>
<td>---------------------------------</td>
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</tr>
<tr>
<td>Bloom syndrome</td>
<td>1/40,000</td>
<td>1/100</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Mucolipidosis IV</td>
<td>1/62,500</td>
<td>1/127</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>1/900</td>
<td>1/15</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Familial hyperinsulinism</td>
<td></td>
<td>1/52</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Glycogen storage disease type I</td>
<td></td>
<td>1/71</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>1/92</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td></td>
<td>1/81</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Usher syndrome</td>
<td>&lt;= 1/40</td>
<td></td>
<td></td>
<td>C</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; ACOG: American College of Obstetricians and Gynecologists; C: should be considered; R: recommended.

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”). Evidence to support the clinical utility of 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. 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. 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.

Section Summary: Risk-Based Carrier Screening

Risk-based carrier screening involves testing for a defined set of pathogenic variants for specified conditions. The clinical validity is sufficiently defined and reflected in estimated residual risk. Numerous studies have shown that reproductive decisions were affected by results from targeted risk-based carrier screening. In addition, ACOG and ACMG consider risk-based carrier screening an established practice and have issued guidance on targeted risk-based screening. There is sufficient evidence to support the clinical utility of targeted risk-based screening.

Expanded Carrier Screening

Clinical Context and Test Purpose

The purpose of ECS is to identify asymptomatic individuals who are heterozygous for serious or lethal recessive single-gene disorders with the purpose of determining the risk of conceiving an affected child and inform reproductive decisions. Expanded carrier screening panels screen for carrier status in a prospective or expectant parent for multiple conditions for which that individual is not known to be at risk based on family history or ethnic background.

The question addressed in this evidence review is: Does the use of ECS improve the net health outcome of asymptomatic individuals at either increased risk or population risk of having offspring with inherited recessive single-gene disorders?

The following PICOTS were used to inform literature selection.
Patients
The relevant population of interest are individuals or couples either at increased risk or population risk for having offspring with inherited gene disorders. Individuals at elevated risk for the purposes of expanded carrier screening include:

- Individuals at increased risk due to race, ethnicity, or family history
- Families that carry a single-gene variant indicative of impairment in DNA repair mechanism
- Individuals with a history of pregnancy loss not explained by a physiologic condition
- History of infertility (after standard work-ups to identify cause)

Interventions
The intervention of interest is ECS.

Comparators
The comparator of interest is targeted carrier screening.

Outcomes
The primary outcome of interest is reproductive decision making.

A beneficial outcome of a true test result is an informed reproductive decision that is consistent with prospective parent(s)’ personal preferences and values. Informed reproductive decisions can include those concerning preimplantation genetic diagnosis, in vitro fertilization, not having a child, invasive prenatal testing, adoption, or pregnancy termination.

A harmful outcome is a reproductive decision based on an incorrect test or assessment of genotype-phenotype relationship. A false-positive result or incorrect genotype-phenotype association could lead to avoiding or terminating a pregnancy unnecessarily. A false-negative test could lead to an affected offspring.

Timing
Preconception or prenatal periods.

Setting
Carrier screening is performed on DNA which can be sampled (e.g., blood or saliva) in specialists' offices or in tertiary care centers. Genetic counseling is performed by providers who are knowledgeable in genetics.

Study Selection Criteria
For the evaluation of the clinical utility ECS, studies would need to use the test to inform reproductive decisions in asymptomatic individuals who are at risk of having an offspring with inherited recessive single-gene disorders. In addition, because the ACOG and the American College of Medical Genetics and Genomics (ACMG) consider risk-based carrier screening an established practice, guideline recommendations from these organizations will also be included in the evidence discussion.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires 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.

Clinically Valid
For conditions where pathogenic variants would be included in an ECS panel, clinical validity should be similar or approach that of the targeted test. Outside those defined variants, pathogenicity, penetrance, and expressivity together with disease severity require accurate
definition. Subsumed in clinical validity is the effect of a condition's severity on quality of life, impairments, and need for intervention.

In 2017, ACOG made the following recommendations on expanded carrier screening (ECS)\(^{18}\): “Expanded carrier screening does not replace previous risk-based screening recommendations.”

Based on consensus, characteristics of included disorders should meet the following criteria:
- Carrier frequency \(\geq 1/100\)
- Well-defined phenotype
- Detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life
- Not be primarily associated with a disease of adult onset

ACOG provided a detailed example of a panel that includes testing for 22 conditions that meet these criteria: a-thalassemia, ß-thalassemia, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, familial hyperinsulinism, Fanconi anemia C, fragile X syndrome, galactosemia, Gaucher disease, glycogen storage disease type 1A, Joubert syndrome, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease types 1A and 1B, mucolipidosis IV, Niemann-Pick disease type A, phenylketonuria, sickle cell anemia, Smith-Lemli-Opitz syndrome, spinal muscular atrophy, and Tay-Sachs disease.

Evidence on larger ECS panels (approximately 100 to 200 disorders) includes series described in Tables 4 and 5\(^{19, 20, 21, 22}\) and two modeling studies\(^{23, 24}\) that estimated the incremental number of potentially affected fetuses if ECS replaced a risk-based approach. Carrier rates with ECS ranged from 19% to 36% in individuals and from 0.2% to 1.2% of couples. Generally, as the size of the panel increases (risk-based to different sizes of expanded panels), the percentage of patients who are identified as carriers for any recessive disease also increases. With a 218 disorder panel, about 1 in 3 individuals were identified as a carrier of a recessive single-gene disorder. The publications did not specify whether the disorders identified met the ACOG criteria, although Peyser et al commented that some diseases may have late onset as well as variable phenotypes.

### Table 4. Relevant Clinical Validity Studies, Study Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Study Design</th>
<th>Study Population</th>
<th>No. Screened</th>
<th>No. of Couples Screened</th>
<th>Disorders Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terhaar et al (2018)(^{22})</td>
<td>Referred for testing at a commercial lab - indications for testing were not evaluated</td>
<td>Database review</td>
<td>51,584 samples analyzed with a trio panel(^{19}), 19,550 samples analyzed with a standard panel(^{23}), 3,902 samples analyzed with a global panel</td>
<td>75,036</td>
<td>NR</td>
<td>Trio = 3, Standard = 23, Global = 218</td>
</tr>
<tr>
<td>Peyser et al (2018)(^{19})</td>
<td>Infertility clinic</td>
<td>Case series</td>
<td>All female and male patients who did not opt out</td>
<td>4232</td>
<td>1206</td>
<td>100</td>
</tr>
</tbody>
</table>
Study | Setting | Study Design | Study Population | No. Screened | No. of Couples Screened | Disorders Screened
--- | --- | --- | --- | --- | --- | ---
Franasiak et al (2016) | Infertility care center | Chart review | Patients who had elected to receive ECS | 6643 | 3738 | 84

CF: cystic fibrosis; NR: not reported.

Table 5. Relevant Clinical Validity Studies, Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Individual Carriers, n (%)</th>
<th>Couple Carriers, n (%)</th>
<th>Incremental Findings Over Risk-Based TestingN (95% CI)</th>
<th>Incremental Findings Over ACOG Recommended Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terhaar et al (2018)</td>
<td>(35.8%)</td>
<td>NA</td>
<td>35.8% vs. 7.2% for trio</td>
<td>35.8% vs. 13.2% for a 23 gene panel</td>
</tr>
<tr>
<td>Peyser et al (2018)</td>
<td>1243 (29.4%)</td>
<td>15 (1.2%)</td>
<td>884</td>
<td>584</td>
</tr>
<tr>
<td>Franasiak et al (2016)</td>
<td>1666 (25.1%)</td>
<td>8 (0.21%)</td>
<td>NNS 748^d (320 to 2302)</td>
<td></td>
</tr>
<tr>
<td>Lazarin et al (2013)</td>
<td>4423 (18.9%)</td>
<td>127 (NA)</td>
<td>NA</td>
<td>NR</td>
</tr>
</tbody>
</table>

CI: confidence interval; NA: not applicable; NGS: next-generation sequencing; NNS: number needed to screen; NR: not reported.

^a One or more disorders.

^b Hb ß-chain-related hemoglobinopathy (n=3), Achromatopsia, GJB2-related DFNB1 nonsyndromic hearing loss, a-1 antitrypsin deficiency; cystic fibrosis (n=2), Gaucher disease, Familial Mediterranean fever, Pompe disease, Smith–Lemli–Opitz syndrome spinal muscle atrophy, familial dysautonomia C3 with CF, carnitine palmitoyltransferase II deficiency, GJB2-related DFNB1 nonsyndromic hearing loss, Gaucher disease, dihydrolipoamide dehydrogenase deficiency, and fragile X premutation.

^c Excluding a single case of Gaucher disease, NNS would be 934. It was not reported if the couple was of Ashkenazi Jewish descent where targeted screening would likely have been performed.

Haque et al (2016) modeled the potential impact that ECS adoption might have had for a cohort of individuals undergoing testing between January 2012 and July 2015. Data were derived from 346,790 individuals undergoing routine ECS. Tests were performed using genotyping (n=308,668) and NGS (n=38,122). The severity of the 94 conditions included in the ECS panel were considered profound according to literature review and algorithm devised by Lazarin et al (2014). The incremental increase in rate of potentially affected fetuses identified with ECS varied according to self-reported ethnicity. Out of 100,000 screened, the model predicted ECS would identify 392 (95% CI, 366 to 420) affected fetuses versus 175 (95% CI, 164 to 186) with guideline-directed screening in Ashkenazi Jews—a difference of 217. Among African Americans, the incremental increase was 47 in 100,000 (364 vs 317) and for those of Northern European descent, 104 in 100,000 (159 vs 55). The authors concluded that ECS “may increase the detection of carrier status for a variety of potentially serious genetic conditions compared with current recommendations from professional societies. Prospective studies comparing current standard-of-care carrier screening with expanded carrier screening in at-risk populations are warranted before expanded screening is adopted.”

A subsequent report by this group (Beauchamp et al, 2018) compared the detection rate of an ECS sequencing panel (Counsyl) with a targeted family screen.
for maximizing per-disease sensitivity for diseases categorized as severe or profound. Specificity of variant classification was maximized by comparison of variant classification with at least two other labs. In the model, the targeted panel detected approximately half the maximal disease risk while the ECS panel was projected to determine 92% of the total risk, with 183 affected conceptions per 1000,000 U.S. births.

Although the results of these studies are consistent with ECS being able to identify more fetuses potentially affected by conditions than guideline-directed targeted screening, there are caveats to consider, as discussed in the accompanying editorial and subsequent correspondence on the Haque study. Specifically:
There may be limited genotype-phenotype data for the additional disorders included.
The severity of some conditions is variable and accurately informing reproductive decisions potentially problematic (short-chain acyl CoA dehydrogenase deficiency provided as an example).
A disorder such as phenylketonuria is treatable and detected by newborn screening yet included in the panel.
It was also noted that fragile X syndrome screening in the absence of a family history (i.e., risk based) is not recommended by professional guidelines. Widespread screening could have unintended consequences, including unnecessary invasive prenatal testing, labeling of newborns, and for some effectively screening for diseases of adult onset (e.g., premature ovarian failure and tremor-ataxia dementia syndrome among males), which is contrary to accepted ethical convention.
Assessing the pathogenicity of sequence variants for rare disorders can be challenging, even when guidelines are followed, because laboratories may not provide the same interpretations. For example, Amendola et al (2016) compared interpretations of 9 variants (pathogenic to benign associated with Mendelian disorders) among 9 diagnostic laboratories, and 90 variants in 3 of them. They found good concordance between the laboratory’s methods for determining pathogenicity and the ACMG-AMP criteria (Krippendorff’s α=0.91; concordance, 79%). However, across laboratories there was only 34% concordance of either classification system and in 22% differences could have affected medical management.
Strom et al (2011) reported on an example of inclusion of a “nonclassical” CF variant (p.L997F) in a carrier screening panel. From a database of approximately 2500 CF sequencing analyses, 4 compound heterozygous patients carrying a pathogenic CF allele and the p.L997F variant were identified. Of the 4 cases, 3 were asymptomatic at ages between 28 and 60 months. The remaining patient was 10 years old with atypical CF. Another compound heterozygous patient having an allele with the p.L997F variant and another deletion had classical CF. The authors concluded that including the variant in a screening panel could lead to “poorly informed reproductive decisions based on incorrect assumptions.”
As noted by Henneman et al (2016) “There is no general agreement on classification of genetic disorders based on the severity of disease.”

Section Summary: Clinical Validity
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 concerns including: interlaboratory agreement of variant pathogenicity assessment when sequencing identifies rare variants, the validity of disease severity classifications for rare disorders, and the certainty of predicted risk that the offspring will be affected by severe phenotype for all the disorders included in a panel.
Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care.

Direct Evidence
Although direct evidence of clinical utility is optimally provided by studies that compare health outcomes for patients managed with and without the test, this is not reasonably expected for carrier screening.

Chain of Evidence
A chain of evidence that ECS offers greater clinical utility than recommended risk-based approaches, relies both on clinical validity—a well-defined predictable risk that the offspring will be affected by severe phenotype—to ECS must:

1. Correctly identify more carrier couples of severe phenotype conditions than recommended risk-based screening (higher clinical sensitivity while maintaining specificity no change in false positives);
2. Inform reproductive decisions more effectively than recommended risk-based carrier screening.

Several surveys studies evaluated patients’ perspectives and reproductive behaviors concerning ECS (see Table 6 and 7). Populations among the studies differed, with some studies including only women known to be carriers and some studies included all pregnant woman, regardless of carrier status. Due to the heterogeneity of the populations and outcomes, combining and summarizing results would not be appropriate.

Table 6. Characteristics of Observational Studies for Clinical Utility

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Number</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghiossi (2018)30</td>
<td>Retrospective survey</td>
<td>United States</td>
<td>2014 to 2015</td>
<td>Couples in which both partners carry genes for the same recessive disease who had received ECS</td>
<td>537 eligible couples, 64 (12%) completed survey</td>
<td>Action (defined as IVF with PGD or prenatal diagnosis) No action</td>
</tr>
<tr>
<td>Propst (2018)31</td>
<td>Survey</td>
<td>United States</td>
<td>NR</td>
<td>Pregnant women undergoing prenatal counseling prior to an aneuploidy screening</td>
<td>80:40 declined ECS 40 elected ECS</td>
<td>Reasons for declining or electing ECS Reproductive planning</td>
</tr>
<tr>
<td>Johansen Taber et al (2018)32</td>
<td>Retrospective survey</td>
<td>United States</td>
<td>2015 to 2017</td>
<td>Women for which both partners carry genes for the same recessive disease who had received</td>
<td>1701 eligible couples who were at risk (78 conditions), 391 women completed the survey</td>
<td>Reproductive planning</td>
</tr>
</tbody>
</table>
Table 7. Results of Observational Studies for Clinical Utility

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghiossi (2018)</td>
<td>60% reported taking action (IVF with PGD or prenatal diagnosis) following ECS results; 40% reported taking no action following ECS results</td>
</tr>
<tr>
<td>Propst (2018)</td>
<td>Reasons for declining ECS: not at risk (77%), small chance that both in couple are carriers (60%), results would not change reproductive planning (37%), too anxious if carrier test was positive (27%); Reasons for electing ECS: want to know risk (90%), want all information available about genetic risk (72%), want to make informed reproductive decisions (61%), want to prepare for special needs child (33%); Reproductive decision if fetus was affected: unsure (43%), would continue pregnancy (34%), and would likely terminate (24%).</td>
</tr>
<tr>
<td>Johansen Taber et al (2018)</td>
<td>77% of patients screened before becoming pregnant planned or pursued actions to avoid having affected offspring (91% for a profound condition, 77% for a severe condition, and 65% for a moderate condition); 37% of patients screened during pregnancy pursued prenatal diagnostic testing; Reasons for declining prenatal testing were fear of miscarriage, belief that termination would not be pursued in the event of a positive diagnosis, or perception that the risk of an affected pregnancy was low.</td>
</tr>
</tbody>
</table>

ECS: expanded carrier screening; IVF: invitro fertilization; PGD: preimplantation genetic diagnosis.

Section Summary: Clinical Utility

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Evidence to support the clinical validity of ECS beyond established risk-based recommendations is limited and accompanied by concerns regarding interlaboratory agreement 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.

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 (ECS), 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 ECS identifies more carriers and more potentially affected fetuses. However, evidence to support the clinical validity of ECS 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.

Supplemental Information
Practice Guidelines and Position Statements

Expanded Carrier Screening Recommendations
American College of Obstetricians and Gynecologists
In 2017, ACOG made the following recommendations on expanded carrier screening (ECS)\textsuperscript{18}:

“Ethnic-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Each obstetrician-gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. After counseling, a patient may decline any or all carrier screening.”

“Expanded carrier screening does not replace previous risk-based screening recommendations.”

Based on “consensus,” characteristics of included disorders should meet the following criteria:
- Carrier frequency $\geq 1/100$
- Well-defined phenotype
- Detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life
- Not be primarily associated with a disease of adult onset

ACOG also noted that ECS panels may not offer the most sensitive detection method for some conditions such as Tay-Sachs disease (i.e., they will miss carrier state in up to 10% of low-risk populations) or hemoglobinopathies.

In 2015, a joint statement on ECS was issued by ACOG, ACMG, the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine.\textsuperscript{2} The statement was not intended to replace current screening guidelines but to demonstrate an approach for health care providers and laboratories seeking to or currently offering ECS panels. Some points considered included the following:
- Expanded carrier screening panels include most of the conditions recommended in current guidelines. However, molecular methods used in expanded carrier screening are not as accurate as methods recommended in current guidelines for the following conditions:
  - Screening for hemoglobinopathies requires use of mean corpuscular volume and hemoglobin electrophoresis
  - Tay-Sachs disease carrier testing has a low detection rate in non-Ashkenazi populations using molecular testing for the three common Ashkenazi mutations. Currently, hexosaminidase 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.
Expanded carrier screening can be performed by genotyping or by DNA sequencing. Genotyping searches for known pathogenic and likely pathogenic variants. Sequencing analyzes the entire coding region of the gene and identifies alterations from the normal sequence. Although genotyping includes only selected variants, sequencing has the potential to identify not only benign, but also likely benign variants. Sequencing also can identify variants of uncertain significance.

Gene panels should only include "genes and variants" with a well-understood relationship with a phenotype. When the carrier frequency and detection rate are both known, residual risk estimation should be provided in laboratory reports.

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

The statement also included a set of recommendations for screened conditions:

- The condition being screened for should be a health problem that encompasses one or more of the following:
  - Cognitive disability
  - Need for surgical or medical intervention
  - Effect on quality of life
- Conditions for which a prenatal diagnosis may result in:
  - Prenatal intervention to improve perinatal outcome and immediate care of the neonate
  - Delivery management to optimize newborn and infant outcomes such as immediate, specialized neonatal care
  - Prenatal education of parents regarding special needs care after birth; this often may be accomplished most effectively before birth

American College of Medical Genetics and Genomics

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:

- 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.

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.

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.

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.

ECS tests must comply with the American College of Medical Genetics and Genomics 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 herein but are in evidence reviews for each condition (see Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers and Genetic Testing for Hereditary Hemochromatosis, respectively).

**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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 8.

Table 8. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02742116</td>
<td>Evaluation of the Implementation of Expanded Carrier Screening Before Pregnancy in Hong Kong</td>
<td>100</td>
<td>Oct 2016</td>
</tr>
<tr>
<td>NCT01902901</td>
<td>Clinical Implementation of Carrier Status Using Next Generation Sequencing</td>
<td>400 384</td>
<td>May 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
Appendix

Appendix Table 1. Categories of Genetic Testing

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual's germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td></td>
</tr>
<tr>
<td>4. Testing of an affected individual's germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td>X</td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td>X</td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
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<tr>
<td>5d. In utero testing: familial variants</td>
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<tr>
<td>5e. In utero testing: other</td>
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<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

Appendix 1. 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 1 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 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 variant 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 variant that causes a disorder who exhibit clinical symptoms of that disorder.

Residual Risk
The risk that an individual is a carrier of a disease, but testing for carrier status of the disease is negative (e.g., if the individual carries a pathogenic variant not included in the test assay).

References


Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- Physician order for genetic test
- Name and description of genetic test
- Name of laboratory that performed the test
- Any available evidence supporting the clinical validity/utility of the specific test
- CPT codes billed for the particular genetic test
- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - Family history if applicable
  - How test result will impact clinical decision making

Post Service

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81243</td>
<td>FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles</td>
</tr>
<tr>
<td>81412</td>
<td>Ashkenazi Jewish associated disorders (e.g., 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</td>
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<tr>
<td>81443</td>
<td>Genetic testing for severe inherited conditions (e.g., cystic fibrosis, Ashkenazi Jewish-associated disorders [e.g., Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (e.g., ACADM, ARSA, ASPA, ATP7B, BCSD1, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC,</td>
<td></td>
</tr>
</tbody>
</table>
### Policy History

This section provides a chronological history of the activities, updates, and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/01/2017</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/01/2017</td>
<td>Policy title change from Carrier Testing for Genetic Diseases</td>
<td>Medical Policy Committee</td>
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<tr>
<td></td>
<td>Policy revision with position change</td>
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</tr>
<tr>
<td>10/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2019</td>
<td>Policy revision without position change Coding update</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2019</td>
<td>Administrative Update - Policy statement clarification Coding update</td>
<td>Administrative Review</td>
</tr>
</tbody>
</table>

### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.