Prenatal Carrier Screening for Genetic Diseases

<table>
<thead>
<tr>
<th>Policy Number:</th>
<th>Current Effective Date:</th>
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<tbody>
<tr>
<td>MM.02.033</td>
<td>November 01, 2019</td>
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<table>
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<tr>
<th>Lines of Business:</th>
<th>Original Effective Date:</th>
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<tr>
<td>HMO; PPO, QUEST Integration</td>
<td>February 01, 2017</td>
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<thead>
<tr>
<th>Place of Service:</th>
<th>Precertification:</th>
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<tbody>
<tr>
<td>Outpatient</td>
<td>Required, see Section V</td>
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I. Description
Carrier screening is performed to identify individuals at risk of having offspring with inherited recessive single-gene disorders. Carriers are usually not at risk of developing the disease, but can pass pathogenic variants to their offspring. Carrier testing may be performed in the prenatal or preconception periods.

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.

II. Policy Criteria
A. Prenatal Carrier Screening for the following conditions is covered (subject to Limitations and Administrative Guidelines)
   1. Cystic Fibrosis (CF)*
   2. Spinal Muscular Atrophy (SMA)*
   3. Fragile X syndrome*
   4. Hemoglobinopathies (sickle cell, α- and β-thalassemia)
   5. Ashkenazi associated conditions*

* Covered per ACOG Recommendations for Risk-Based Screening- See Table 2.
B. Prenatal Carrier screening for genetic diseases is covered (subject to Limitations and Administrative Guidelines) when one of the following criteria is met (excluding CF and SMA):
   1. One or both individuals have a first- or second-degree relative who is affected OR
   2. One individual is known to be a carrier OR
   3. 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
   4. 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; and
   5. 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; and
   6. The genetic test has adequate clinical validity to guide clinical decision making and residual risk is understood (see Policy Guidelines 2 section); and
   7. An association of the marker with the disorder has been established.

C. Characteristics of included disorders should meet the following criteria:
   1. Carrier frequency ≥1/100
   2. Well-defined phenotype
   3. Detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life
   4. Not be primarily associated with a disease of adult onset.

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
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 (eg, 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.

<table>
<thead>
<tr>
<th>Table PG1. Nomenclature to Report on Variants Found in DNA</th>
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<tbody>
<tr>
<td><strong>Previous</strong></td>
</tr>
<tr>
<td>Mutation</td>
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<tr>
<td>Variant</td>
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<tr>
<td>Familial variant</td>
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</table>

<table>
<thead>
<tr>
<th>Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variant Classification</strong></td>
</tr>
<tr>
<td>Pathogenic</td>
</tr>
<tr>
<td>Likely pathogenic</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
</tr>
<tr>
<td>Likely benign</td>
</tr>
<tr>
<td>Benign</td>
</tr>
</tbody>
</table>

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

**Genetic Counseling**

Genetic counseling is appropriate for patients who meet the policy criteria for testing. One Pre- and one post-test genetic counseling by a physician or a licensed or certified genetic counselor is covered for patients who meet the above criteria for genetic testing.
III. Limitations
   A. All targeted screening not meeting any of the above criteria is not covered as it is not known to be effective in improving long-term health outcomes.
   B. Expanded carrier screening panels are not covered as they are not known to be effective in improving long-term health outcomes (see Policy Guidelines 3 section)

IV. Administrative Guidelines
   A. Precertification are not required for Cystic Fibrosis Screening (CF) CPT 81220 and Spinal Muscular Atrophy (SMA) CPT 81329. ACOG recommends that CF and SMA carrier screening should be offered to all women considering pregnancy or are pregnant.
   B. Precertification is required for all other prenatal 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.
   C. Applicable codes are as follows:
      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.

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; common variant</td>
</tr>
<tr>
<td>81243</td>
<td>FMR1 (fragile X mental retardation 1) (e.g. fragile X mental retardation) gene analysis; evaluation to detect abnormal alleles</td>
</tr>
<tr>
<td>81255</td>
<td>HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G&gt;C, G269S)</td>
</tr>
<tr>
<td>81257</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and constant spring)</td>
</tr>
<tr>
<td>81329</td>
<td>Smn1 (survival of motor neuron 1, telomeric) (e.g, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes smn2 (survival of motor neuron 2, centromeric) analysis, if performed</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>
</tr>
<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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</tbody>
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<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
</tr>
<tr>
<td>S3845</td>
<td>Genetic testing for alpha-thalassemia</td>
</tr>
<tr>
<td>S3846</td>
<td>Genetic testing for hemoglobin E beta-thalassemia</td>
</tr>
<tr>
<td>S3850</td>
<td>Genetic testing for sickle cell anemia</td>
</tr>
</tbody>
</table>

V. Scientific 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 Laboratories</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>
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<tr>
<td>Igenomix</td>
<td>Igenomix</td>
<td>Spain</td>
<td>633</td>
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<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>
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<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>
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<tr>
<td>Progenity</td>
<td>Progenity Inc</td>
<td>US</td>
<td>230</td>
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<tr>
<td>Recombine</td>
<td>CooperGenomics</td>
<td>US</td>
<td>314</td>
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<tr>
<td>Academic Medical Center Amsterdam</td>
<td></td>
<td>Netherlands</td>
<td>50</td>
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</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.

**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**
This evidence review was originally created in November 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 1, 2018 (see Appendix Table 1 for genetic testing categories).

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 Askenazi 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><strong>Cystic fibrosis</strong></td>
<td></td>
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<tr>
<td>ACOG</td>
<td>“Cystic fibrosis carrier screening should be offered to all women considering pregnancy or are pregnant.”</td>
<td>2017</td>
</tr>
<tr>
<td>ACMG</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><strong>Spinal muscular atrophy</strong></td>
<td></td>
<td></td>
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<tr>
<td>ACOG</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>ACMG</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><strong>Tay-Sachs disease</strong></td>
<td></td>
<td></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><strong>Fragile X syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACOG</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</td>
<td>2017</td>
</tr>
</tbody>
</table>
who are considering pregnancy or are currently pregnant. If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an FMR1 premutation.”

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.

ACOG and ACMG 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 Descent

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<thead>
<tr>
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</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>
</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>1/52</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Glycogen storage disease type I</td>
<td>1/71</td>
<td></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>1/81</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Usher syndrome</td>
<td>≤ 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 (ie, increases “reproductive autonomy and choice”). Evidence to support the clinical utility of carrier screening for conditions with the highest carrier rates (eg, Tay-Sachs disease, CF) among specific ethnic groups is robust concerning the effect on reproductive decision making. For example, early studies of Tay-Sachs carrier screening in Ashkenazi Jews demonstrated a marked impact on reproductive decisions and, after some 4 decades of ethnicity-based carrier screening, most Tay-Sachs disease cases occur in non-Jewish individuals. 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 (eg, 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):
“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 ≥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: α-thalassemia, β-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, and two modeling studies 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>
<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 19,550 samples analyzed with a standard panel 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>
<tr>
<td>Franasiak et al (2016)20</td>
<td>Infertility care center</td>
<td>Chart review</td>
<td>Patients who had elected to receive ECS</td>
<td>6643</td>
<td>3738</td>
<td>84</td>
</tr>
</tbody>
</table>

CF: cystic fibrosis; NR: not reported.

* By obstetricians, family practitioners, geneticists, genetics counselors, perinatologists, and reproductive endocrinologists.

<table>
<thead>
<tr>
<th>Study</th>
<th>Individual Carriers, n (%)</th>
<th>Couple Carriers, n (%)</th>
<th>Incremental Findings Over Risk-Based Testing N (95% CI)</th>
<th>Incremental Findings Over ACOG Recommended Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terhaar et al (2018)22</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>
</tbody>
</table>
Prenatal Carrier Screening for Genetic Diseases

<table>
<thead>
<tr>
<th>Study</th>
<th>N (Losses)</th>
<th>CI 95%</th>
<th>Number Needed to Screen (NNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peyser et al (2018)</td>
<td>1243 (29.4%)</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 (320 to 2302)</td>
</tr>
<tr>
<td>Lazarin et al (2013)</td>
<td>4423 (18.9%)</td>
<td>127 (NA)</td>
<td>NA</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 β-chain-related hemoglobinopathy (n=3), Achromatopsia, GJB2-related DFNB1 nonsyndromic hearing loss, α-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.
cExcluding 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.

d 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. The ECS panel was designed 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 is that fragile X syndrome screening in the absence of a family history (ie, 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 (eg, 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 women, regardless of carrier status. Due to the heterogeneity of the populations and outcomes, combining and summarizing results would not be appropriate.

<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>
</table>
| Ghiossi (2018)30       | Retrospective survey | United States | 2014 to 2015  | Couples in which both partners carry genes for the same recessive disease who had received ECS | 537 eligible couples, 64 (12%) completed survey | · Action (defined as IVF with PGD or prenatal diagnosis)  
                           · No action |
| Propst (2018)31        | Survey       | United States | NR            | Pregnant women undergoing prenatal counseling prior to an aneuploidy screening | 80: 40 declined ECS 40 elected ECS | · Reasons for declining or electing ECS  
                           · Reproductive planning |
| Johansen Taber et al (2018)32 | Retrospective survey | United States | 2015 to 2017  | Women for which both partners carry genes for the same recessive disease who had received ECS; 54% were for IVF | 1701 eligible couples who were at risk (78 conditions), 391 women completed the survey | · Reproductive planning |

ECS: expanded carrier screening; IVF: invitro fertilization; NR: not reported; PGD: preimplantation genetic diagnosis.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Results</th>
</tr>
</thead>
</table>
| Ghiossi (2018)30 | · 60% reported taking action (IVF with PDG or prenatal diagnosis) following ECS results  
                        · 40% reported taking no action following ECS results |
| Propst (2018)31 | · 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%) |
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.

VI. Supplemental Information
Expanded Carrier Screening Recommendations
American College of Obstetricians and Gynecologists
In 2017, ACOG made the following recommendations on expanded carrier screening (ECS):

“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 ≥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. 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:
  a. Screening for hemoglobinopathies requires use of mean corpuscular volume and hemoglobin electrophoresis.
  b. 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....

- ECS 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:

1. “The condition being screened for should be a health problem that encompasses one or more of the following:
   b. Need for surgical or medical intervention.
Effect on quality of life.

d. Conditions for which a prenatal diagnosis may result in:
   i. Prenatal intervention to improve perinatal outcome and immediate care of the neonate.
   ii. Delivery management to optimize newborn and infant outcomes such as immediate, specialized neonatal care.
   iii. 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:

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 non-maleficence.

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 non-maleficence.

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 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
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 Genetic Testing - BRCA).

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>Ongoing</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>384</td>
<td>May 2018</td>
</tr>
</tbody>
</table>

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


