

<b>2.04.107</b>	<b>Carrier Screening for Genetic Diseases</b>		
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<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 19

## Policy Statement

Carrier screening for genetic diseases 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**.

Expanded carrier screening panels are considered **investigational** (see Policy Guidelines 3 section).

## 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.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

Variant Classification	Definition
<b>Pathogenic</b>	Disease-causing change in the DNA sequence
<b>Likely pathogenic</b>	Likely disease-causing change in the DNA sequence
<b>Variant of uncertain significance</b>	Change in DNA sequence with uncertain effects on disease
<b>Likely benign</b>	Likely benign change in the DNA sequence
<b>Benign</b>	Benign change in the DNA sequence

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

### 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**

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*

**Description**

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.<sup>1</sup> Some diseases have limited impact on either length or quality of life, while others are uniformly fatal in childhood.

#### Carrier Screening

Carrier screening is testing asymptomatic individuals to identify those who are heterozygous for serious or lethal single-gene disorders with the purpose of informing the risk of conceiving an affected child “to provide ... information to optimize pregnancy outcomes based on ... personal preferences and values.”<sup>2</sup> Risk-based carrier screening is performed in individuals having an increased risk based on population carrier prevalence, and personal or family history. Conditions selected for screening can be based on ethnicities at high risk (e.g., Tay-Sachs disease in Ashkenazi Jews) or may be pan-ethnic (e.g., screening for cystic fibrosis carriers). Ethnicity-based screening for some conditions has been offered for decades and, in some cases, has reduced the prevalence of diseases. For example, a 90% reduction in Tay-Sachs disease followed introduction carrier screening in the 1970s in the United States and Canada.<sup>3</sup> In addition, the U.S. population has become increasingly ethnically intermarried<sup>4,5</sup>—a phenomenon the American College of Obstetricians and Gynecologists noted when offering a recommendation in 2005 for pan-ethnic cystic fibrosis carrier screening.<sup>6</sup>

While methods for carrier screening of conditions individually may have been onerous in the past, contemporary molecular techniques including next-generation sequencing allow simultaneously identifying carriers of a wide range of disorders efficiently and inexpensively.

#### Expanded Carrier Screening

Expanded carrier screening (ECS) involves screening individuals or couples for disorders in many genes (up to 100s). The disorders included may also span a range of disease severity or phenotype. Arguments for ECS include potential issues in assessing ethnicity, ability to identify more potential conditions, efficiency, and cost. Uncertain are the possible downsides of screening individuals at low risk, including a potential for incorrect variant ascertainment and the consequences of screening for rare single-gene disorders in which the likely phenotype may be uncertain (e.g., due to variable expressivity and uncertain penetrance). The list of conditions included in ECS panels is not standardized. Although ECS panels would include conditions assessed in risk-based screening, ECS panels 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

The most recent literature update was performed through March 9, 2017 (see Appendix Table 1 for genetic testing categories).

The evaluation of the a genetic carrier screening test focuses on 3 main principles: (1) analytic validity (the technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (the performance characteristics of a test [sensitivity, specificity, positive and negative predictive values] in predicting incident disease [i.e., must take into account penetrance and expressivity as well as condition severity]); and (3) clinical utility (i.e., demonstrating that the information can be used to inform reproductive decisions).

## **Risk-Based Carrier Screening**

### **Clinical Context and Test Purpose**

The purpose of carrier screening is testing asymptomatic individuals to identify those who are heterozygous for serious or lethal single-gene disorders with the purpose of informing the risk of conceiving an affected child and to inform reproductive decisions.

Risk-based carrier screening can be pan-ethnic (e.g., cystic fibrosis [CF], spinal muscular atrophy) or based on disease and carrier risk determined by family history, ethnicity, and race. Pan-ethnic screening is recommended when carrier rates in the general population approach or exceed those judged to offer clinical utility and/or ethnicity may be difficult to evaluate. Risk-based carrier screening is performed by genotyping for a set of defined variants (in contrast to identifying variants by sequencing an entire gene).

The question addressed in this evidence review is: What is the evidence supporting the analytic validity, clinical validity, and clinical utility of risk-based carrier screening?

The following PICOTS were used to inform literature selection.

### **Patients**

The relevant populations of interest are individuals or couples in either the preconception or prenatal periods.

### **Interventions**

The intervention of interest is risk-based carrier screening.

### **Comparators**

The comparator of interest is no carrier screening.

### **Outcomes**

The primary outcome of interest is reproductive decision making, with test accuracy and validity required to inform decisions.

The outcome sought is an informed reproductive decision consistent with prospective parent(s) personal preferences and values. Reproductive decisions informed 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. For example, a false-positive result or incorrect genotype-phenotype association could lead to avoiding or terminating a pregnancy unnecessarily, a false negative to an affected offspring.

### **Setting**

Preconception or prenatal periods.

### **Analytic Validity**

The analytic validity of many targeted carrier screening tests has been reported to be high. For example, 1 major laboratory has reported that the analytic sensitivities and specificities of its CF 165-variant panel and their Ashkenazi Jewish panel (which includes testing for 51 variants and 16 conditions) are all 99% (both approved by the New York State Department of Health).<sup>7</sup> Depending on the population and disease, not all risk-based carrier screening relies on testing for genetic variants—e.g., the Hexosaminidase A Enzyme Assay for Tay-Sachs disease or screening for hemoglobinopathies. The analytic validity of these tests performed in Clinical Laboratory Improvement Amendments (CLIA)—or College of American Pathologists (CAP)—certified labs is anticipated to be high. For genetic assays of pathogenic variants in risk-based carrier screening, analytic validity is similarly anticipated to be high.

**Clinical Validity**

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.<sup>1</sup> 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%).<sup>7</sup> 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.

**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”<sup>1</sup>). Evidence to support the clinical utility 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.<sup>3,8-10</sup> For example, early studies of Tay-Sachs carrier screening in Ashkenazi Jews demonstrated a marked impact on reproductive decisions<sup>8,10</sup> and, after some 4 decades of ethnicity-based carrier screening, most Tay-Sachs disease cases occur in non-Jewish individuals.<sup>9</sup> 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.<sup>11</sup> For inherited single-gene disorders where carrier rates are of similar magnitude, recommendations to offer screening have therefore arguably a convincing rationale, even if partially based indirectly on results from other conditions.

**Section Summary: Risk-Based Carrier Screening**

Risk-based carrier screening involves testing for a defined set of pathogenic variants for specified conditions. The analytic validity is expected to be high in qualified laboratories. The clinical validity is sufficiently defined and reflected in estimated residual risk. There is sufficient evidence to support the clinical utility of risk-based screening.

**Expanded Carrier Screening****Clinical Context and Test Purpose**

The purpose of expanded carrier screening (ECS) is testing asymptomatic individuals to identify those who are heterozygous for many serious or lethal single-gene disorders with the purpose of informing the risk of conceiving an affected child and to inform reproductive decisions.

The question addressed in this evidence review is: What is the evidence supporting the analytic validity, clinical validity, and clinical utility of ECS?

The following PICOTS were used to inform literature selection.

**Patients**

The relevant populations of interest are individuals or couples in either the preconception or prenatal periods.

**Interventions**

The intervention of interest is risk-based carrier screening.

### **Comparators**

The comparator of interest is no carrier screening.

### **Outcomes**

The primary outcome of interest is reproductive decision making, with test accuracy and validity required to inform decisions.

The outcome sought is an informed reproductive decision consistent with prospective parent(s) personal preferences and values. Reproductive decision informed 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. For example, a false-positive result or incorrect genotype-phenotype association could lead to avoiding or terminating a pregnancy unnecessarily, a false negative to an affected offspring.

### **Setting**

Preconception or prenatal periods.

### **Analytic Validity**

Commercial ECS panels could include sequencing by NGS and targeted testing. Hallam et al (2014) reported analytic validation of an ECS NGS panel (Good Start Genetics).<sup>12</sup> From 11,691 in vitro fertilization patients, 447 pathogenic variants were identified in carriers—87 different variants across 14 genes. Sanger sequencing was used as the reference standard. The authors reported a series of studies to evaluate NGS technical performance characteristics: accuracy, lot-to-lot variability, limit of detection, reproducibility, interfering substances, and blinded accuracy. Performance characteristics were generally high. The assay did generate 9 false-positive variant calls in 6.4 million base pairs. Srinivasan et al (2010) described performance of version 1.0 (current offering is v.2.0) of the Counsyl Family Prep Screen in testing for over 100 disorders using a median of 147 positive and 525 negative samples per variant.<sup>13</sup> They reporting a false-positive call rate of 0.994 and false-negative rate of 0.002.

Establishing and reporting the analytic validity of relevant parameters for NGS across the genes and variants of interest presents challenges. Moreover, accuracy of variant ascertainment depends on many factors (e.g., genomic region, read depth, variant type, bioinformatics pipeline)<sup>14</sup>; for those not within those assessed in studies of targeted testing, variants will require careful evaluation given the potential consequences of inaccuracies.

### **Clinical Validity**

For conditions where pathogenic variants would be included in a risk-based genotyping carrier test, clinical validity should be similar or approach that of the targeted test. Outside those defined variants (or when genotyping includes only others with strong evidence supporting pathogenicity), for the purposes of carrier screening 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. Current American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) guidelines have provided recommendations for defining the pathogenicity of sequence variants.<sup>15</sup> However, 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  $\alpha=0.91$ ; concordance, 79%).<sup>16</sup> However, across laboratories

there was only 34% concordance of either classification system and in 22% differences could have affected medical management.

Pertaining to assessing the severity of disorders, Lazarin et al (2014) developed a classification schema to judge phenotype severity to select conditions for inclusion in an expanded panel.<sup>17</sup> The study was described as a “pilot test” of the hypothesis that “diseases with characteristics of lower impact would be rated as less severe.” Classifications of severity—profound, severe, moderate, and mild—were developed from a survey of health care providers who ordered carrier screening tests, although they might not have had expert knowledge concerning the diseases they assessed. A total of 3185 individuals would invited to participate; 192 (6.4%) responded, of whom 70.3% were genetics counselors. Whether the sample was representative of those invited was not reported. Surveys took an average of under 6 minutes to complete. Participants were provided characteristics of diseases to complete the survey. Four tiers of disease characteristics were identified (tier 1 being the most severe, tier 4 the least severe) based on average severity ratings for consequences of shortened life span, intellectual disability, impaired mobility, sensory impairment, and reduced fertility, along with availability of treatment and variable expressivity. After establishing these tiers, the same individuals rated severity for 3 sets of 5 selected inherited diseases (3 included diseases were included in ACOG or ACMG screening guidelines) as “mild,” “moderate,” “severe,” or “profound.” None of the 15 diseases were classified as “mild,” 2 were rated as “moderate,” and the remaining 13 diseases “severe” or “profound.” From these results, an algorithm was developed that allowed classification of disease severity for many conditions.

Although the study achieved its goal, several issues require considering in the generalizability of the results and algorithm. First, participants’ degree of familiarity with the clinical manifestations across the conditions is unclear. Second, agreement among raters was not reported nor was validation described. Finally, it is unclear whether the schema would be supported by the general medical community; as recently noted by Henneman et al (2016) “There is no general agreement on classification of genetic disorders based on the severity of disease.”<sup>1</sup>

Finally, Strom et al (2011) reported on an example of inclusion of a “nonclassical” CF variant (p.L997F) in a carrier screening panel.<sup>18</sup> In a database of approximately 2500 CF sequencing analyses, the authors identified 4 compound heterozygous patients carrying a pathogenic CF allele and the p.L997F variant—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.”

### **Clinical Utility**

In addition to clinical validity—a well-defined predictable risk that the offspring will be affected by severe phenotype—to offer greater clinical utility than recommended risk-based approaches, ECS must:

1. Correctly identify more carrier couples of those 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.

Relevant evidence identified includes 3 studies<sup>19-21</sup> listed in Table 1, and a modeling study<sup>22</sup> that estimated the incremental number of potentially affected fetuses if ECS replaced a risk-based approach.



Table 1. Relevant Clinical Utility Studies

Study	Setting	No. Screened	Ashkenazi Jews	Individual Carriers, n (%) <sup>a</sup>	No. of Couples Screened	Couple Carriers, N (%)	Incremental NNS Couples Over Risk-Based Testing N (95% CI) <sup>b</sup>	Disorders
Arjunan et al (2016)	Jewish genetics center	506	85.6%	288 (56.9%)	185	8 (4.3%)	46 <sup>c</sup> (18 to 169)	84 + fragile X
Lazarin et al (2013)	Referred for routine testing <sup>d</sup>	23,453	10.3%	4423 (18.9%)	NR	127 (NA)	NA	108
Franasiak et al (2016)	Infertility care center	6643	NR	1666 (25.1%)	3738	8 (0.21%)	748 <sup>e</sup> (320 to 2302)	<ul style="list-style-type: none"> <li>• 102 variants by genotyping (53.8% of patients)</li> <li>• 117 variants by genotyping (42.4% of patients)</li> <li>• Genotyping/NGS (3.8% of patients)</li> </ul>

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

<sup>a</sup> One or more disorders.

<sup>b</sup> Calculated.

<sup>c</sup> Calculated assuming 4 of the 5 couples carrying the same variant would have gone undetected absent expanded carrier screening (a couple carrying Gaucher disease excluded owing to likely inclusion in Ashkenazi Jewish panels).

<sup>d</sup> By obstetricians, family practitioners, geneticists, genetics counselors, perinatologists, and reproductive endocrinologists.

<sup>e</sup> 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.

Arjunan et al (2016) reported results from screening 506 individuals at a center for Jewish genetics Center in Chicago—almost all (85.6%) of Ashkenazi Jewish descent. Samples were analyzed by sequencing, targeted genotyping, triplet repeat detection, and for copy number variants. Genotyping included variants for 19 Ashkenazi Jewish disorders and 65 autosomal recessive conditions. Sequencing identified 434 pathogenic variants and genotyping 312. Compared with genotyping, ECS with sequencing identified 2 additional couple who were carriers of the same pathogenic variant. Both approaches were based on expanded panels, but the results suggested sequencing may increase the diagnostic yield in individuals of Ashkenazi Jewish descent.

Lazarin et al (2013) reported on the carrier status of an ethnically diverse sample of 23,453 individuals.<sup>21</sup> Individuals were referred for “routine” testing by obstetricians, family practitioners, geneticists, genetics counselors, perinatologists, and reproductive endocrinologists. Using the Counsyl screening platform, they tested for 417 disease-causing variants associated with 108 recessive diseases. Of the individuals tested, 5633 (24%) were heterozygous for at least 1 condition, and 5.2% identified as carriers for multiple disorders. Of 127 carrier couples identified (i.e., pairs of individuals identified as partners by self-report who were both found to share

heterozygosity for at least 1 disease), 47 (37%) were for  $\alpha_1$ -antitrypsin deficiency, a condition that has reduced penetrance, variable severity, and uncertain clinical presentation in the newborn period and into adulthood. The American Thoracic Society and European Respiratory Society have discouraged genetic testing for  $\alpha_1$ -antitrypsin deficiency in asymptomatic adults with no increased risk for this disease.<sup>23</sup>

Franasiak et al (2016) evaluated ECS among 6643 individuals (3738 couples) at a single infertility clinic from 2011 to 2014.<sup>20</sup> Most testing was performed using genotyping with sequencing adopted near the end of the study period. A positive test was obtained in 1666 (25.1%) of the individuals and in 8 (0.21%) of couples (all white)—3 with CF, carnitine palmitoyltransferase II deficiency, *GJB2*-related DFNB1 nonsyndromic hearing loss, Gaucher disease, dihydrolipoamide dehydrogenase deficiency, and fragile X premutation. There were prior CF pregnancies in the 3 couples that were CF variant carriers. Outcomes for the fragile X premutation carrier couple were not described. In the other 4 couples, preimplantation genetic diagnosis was performed with births of unaffected children. In the infertility setting, study results are consistent with ECS detecting incrementally more affected couples and impacted reproductive decisions. A total of 748 (95% CI, 320 to 2302) couples (potentially 1 member if sequential testing used) were screened to detect 1 where both members were carriers of a pathogenic variant that could lead to an affected offspring.

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 (including those reported in Lazarin et al [2013]). Tests were performed using genotyping ( $n=308,668$ ) and NGS ( $n=38,122$ ); 78.9% of tests obtained in women. The severity of the 94 conditions included in the ECS panel were considered profound or according to literature review and algorithm devised by Lazarin et al (2014).<sup>17</sup> Analyses were performed using a complex Bayesian model. The incremental increase in rate of potentially affected fetuses identified with ECS varied according to self-reported ethnicity. For example, among Ashkenazi Jews the model predicted ECS would identify 392 in 100,000 affected fetuses (95% CI, 366 to 420) versus 175 (95% CI, 164 to 186) with guideline-directed screening—a difference of 217 in 100,000. Among African Americans, the incremental increase was 47 in 100,000 (364/100,000 vs 317/100,000) and for those of Northern European descent, 104 in 100,000 (159/100,000 vs 55/100,000). 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.” This study was funded by Counsyl.

Although the results are consistent with ECS being able to identify more fetuses potentially affected by conditions than guideline-directed screening, there are caveats to consider, as discussed in the accompanying editorial and subsequent correspondence on the Haque study.<sup>24,25</sup> For one, there may be limited genotype-phenotype data for the additional ultra-rare disorders included. Next, 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. Also noted is 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.

### Section Summary: Expanded Carrier Screening

The analytic validity of ECS panels will depend on the molecular method used; 2 identified studies support the analytic validity for ECS, but variant ascertainment with NGS requires careful evaluation. 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.

### Summary of Evidence

For individuals who are asymptomatic but at risk for having offspring with inherited single-gene disorders who receive risk-based carrier screening, the evidence includes studies supporting analytic validity, clinical validity, and clinical utility. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. Reported analytic validity (technical accuracy) of targeted carrier screening tests is high. Results of 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 asymptomatic but at risk for having offspring with inherited single-gene disorders who receive expanded carrier screening (ECS), the evidence includes studies on analytic validity, clinical validity, and indirectly clinical utility. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. The analytic validity of ECS panels will depend on the molecular method used; 2 identified studies support the analytic validity for ECS, but variant ascertainment with next-generation sequencing requires careful evaluation. Three studies have found that ECS identifies more carriers and potentially affected fetuses. However, evidence to support the clinical validity of ECS beyond risk-based recommendations is limited and accompanied by some 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 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

#### Risk-Based Condition-Specific Screening Recommendations

The American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics and Genomics (ACMG) have issued numerous guidelines on conditions discussed herein. Table 2 provides the recommendations by indication for risk-based screening.

**Table 2. ACOG and ACMG Recommendations for Risk-Based Screening**

Society	Recommendation	Year
<b>Cystic fibrosis<sup>a</sup></b>		
ACOG	"Cystic fibrosis carrier screening should be offered to all women considering pregnancy or are pregnant." <sup>26</sup>	2017
ACMG	Current ACMG guidelines use a 23-variant panel and were developed after assessing the initial experiences on implementation of cystic fibrosis screening into clinical practice. Using the 23-variant panel, the detection rate is 94% in the Ashkenazi Jewish population and 88% in the non-Hispanic white general population. <sup>27</sup>	2013
<b>Spinal muscular atrophy<sup>b</sup></b>		
ACOG	"Screening for spinal muscular atrophy should be offered to all women considering pregnancy or are pregnant. In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, SMN1 deletion testing should be recommended for the low-risk partner." <sup>26</sup>	2017
ACMG	Because spinal muscular atrophy is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity. <sup>28</sup>	2013
<b>Tay-Sachs disease</b>		

Society	Recommendation	Year
ACOG	"Screening for Tay-Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French-Canadian, or Cajun descent. Those with a family history consistent with Tay-Sachs disease should also be screened." <sup>26</sup>	2017
<b>Hemoglobinopathies (sickle cell disease, <math>\alpha</math>- and <math>\beta</math>-thalassemia)</b>		
ACOG	"A complete blood count with red blood cell indices should be performed in all women who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of a hemoglobinopathy. Ideally, this testing also should be offered to women before pregnancy. A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent). If red blood cell indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume, hemoglobin electrophoresis also should be performed." <sup>26</sup>	2017
<b>Fragile X syndrome</b>		
ACOG	"Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant. If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an FMR1 premutation." <sup>26</sup>	2017

ACMG: American College of Medical Genetics and Genomics; ACOG: American College of Obstetricians and Gynecologists.

<sup>a</sup> Carrier rates: Ashkenazi Jews 1/24, non-Hispanic white 1/25, Hispanic white 1/58, African American 1/61, Asian American 1/94.

<sup>b</sup> General population carrier rate: 1/40 to 1/60.

### Ashkenazi Jewish Populations

Individuals of Ashkenazi Jewish descent have high carrier rates for multiple conditions—cumulatively between 1 in 4 and 1 in 5 when all disorders are considered.<sup>29</sup> Recommendations for carrier screening for Ashkenazi Jewish individuals by ACOG<sup>26</sup> and ACMG<sup>29</sup> are summarized in 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<sup>26,29</sup>**

Condition	Incidence (Lifetime)	Carrier Rate	ACMG (2008, 2013)	ACOG (2017)
Tay-Sachs disease	1/3000	1/30	R	R
Canavan disease	1/6400	1/40	R	R
Cystic fibrosis	1/2500-3000	1/29	R	R
Familial dysautonomia	1/3600	1/32	R	R
Fanconi anemia (group C)	1/32,000	1/89	R	C
Niemann-Pick disease type A	1/32,000	1/90	R	C
Bloom syndrome	1/40,000	1/100	R	C
Mucopolysaccharidosis IV	1/62,500	1/127	R	C
Gaucher disease	1/900	1/15	R	C
Familial hyperinsulinism		1/52		C
Glycogen storage disease		1/71		C
Joubert syndrome		1/92		C
Maple syrup urine disease		1/81		C
Usher syndrome		≤ 1/40		C

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

### Expanded Carrier Screening Recommendations *American College of Obstetricians and Gynecologists*

In 2017, ACOG made the following recommendations on expanded carrier screening (ECS)<sup>30</sup>:

“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.

ACOG also provided a detailed example of an ECS panel that includes testing for 22 conditions:  $\alpha$ -thalassemia,  $\beta$ -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, mucopolysaccharidosis IV, Niemann-Pick disease type A, phenylketonuria, sickle cell anemia, Smith-Lemli-Opitz syndrome, spinal muscular atrophy, and Tay-Sachs disease.

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.<sup>2</sup> 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  $\alpha_1$ -antitrypsin, methylene tetrahydrofolate reductase, and hereditary hemochromatosis.

The statement also included a set of recommendations for screened conditions<sup>2</sup>:

1. The condition being screened for should be a health problem that encompasses one or more of the following:
  - a. Cognitive disability.
  - b. Need for surgical or medical intervention.
  - c. 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.<sup>31</sup> For a particular disorder to be included in carrier screening, the following criteria should be met:

1. Disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction.
  - The inclusion of disorders characterized by variable expressivity or incomplete penetrance and those known to be associated with a mild phenotype should be optional and made transparent when using these technologies for screening. This recommendation is guided by the ethical principle of nonmaleficence.
2. When adult-onset disorders (disorders that could affect offspring of the individual undergoing carrier screening once offspring reach adult life) are included in screening panels, patients must provide consent to screening for these conditions, especially when there may be implications for the health of the individual being screened or for other family members.
  - This recommendation follows the ethical principles of autonomy and nonmaleficence.
3. For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed.
  - Laboratories should specify in their marketing literature and test results how residual risk was calculated using pan-ethnic population data or a specific race/ethnic group.
  - The calculation of residual risk requires knowledge of 2 factors: one is the carrier frequency within a population, the other is the proportion of disease-causing alleles detected using the specific testing platform. Laboratories using multiplex platforms often have limited knowledge of one or both factors. Laboratories offering expanded carrier screening should keep data prospectively and regularly report findings that allow computation of residual risk estimates for all disorders being offered. When data are inadequate, patient materials must stress that negative results should not be overinterpreted.
4. There must be validated clinical association between the mutation(s) detected and the severity of the disorder.

- Patient and provider materials must include specific citations that support inclusion of the mutations for which screening is being performed.
5. ECS tests must comply with 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 in se evidence reviews for each condition (see 2.04.02 and 2.04.80, 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 4.

**Table 4. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT01902901	Clinical Implementation of Carrier Status Using Next Generation Sequencing	400	May 2017

NCT: national clinical trial.

## Appendix

**Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.107**

Category	Addressed
1. Testing of an affected individual's germline to benefit the individual	
1a. Diagnostic	
1b. Prognostic	
1c. Therapeutic	
2. Testing cancer cells from an affected individual to benefit the individual	
2a. Diagnostic	
2b. Prognostic	
2c. Therapeutic	
3. Testing an asymptomatic individual to determine future risk of disease	
4. Testing of an affected individual's germline to benefit family members	
5. Reproductive testing	
5a. Carrier testing: preconception	X
5b. Carrier testing: prenatal	X
5c. In utero testing: aneuploidy	
5d. In utero testing: familial variants	
5e. In utero testing: other	

Category	Addressed
5f. Preimplantation testing with in vitro fertilization	

## 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).

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### 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 benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) 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.

Type	Code	Description
CPT®	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
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Type	Code	Description
ICD-10 Procedure	None	
ICD-10 Diagnosis	All Diagnoses	

### Policy History

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

Effective Date	Action	Reason
02/01/2017	BCBSA Medical Policy adoption	Medical Policy Committee
06/01/2017	Policy title change from Carrier Testing for Genetic Diseases Policy revision with position change	Medical Policy Committee

### 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](http://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.*