Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the Blue Cross Blue Shield Association

Title: Carrier Screening for Genetic Diseases

Related Policies:	▪ *Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)*

Professional / Institutional
Original Effective Date: January 1, 2024
Latest Review Date:
Current Effective Date: January 1, 2024

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic but at risk for having an offspring with inherited X-linked or autosomal recessive single-gene disorders	Interventions of interest are: • Targeted risk-based carrier screening	Comparators of interest are: • No carrier screening	Relevant outcomes include: • Test validity • Changes in reproductive decision making
Individuals: • Who are either at increased risk or population risk of	Interventions of interest are: • Non-targeted carrier screening panel	Comparators of interest are: • Targeted risk-based carrier screening	Relevant outcomes include: • Test validity

Populations	Interventions	Comparators	Outcomes
having offspring with an inherited X-linked or autosomal recessive genetic disorder			• Changes in reproductive decision making

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.

OBJECTIVE

The objective of this evidence review is to evaluate whether targeted risk-based or non-targeted carrier screening panel testing improves the net health outcomes of individuals at either an increased risk or population risk of inherited X-linked or autosomal recessive single-gene disorders.

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.[1,] 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."[2,] 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 panethnic. 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 U.S. and Canada.[3,] An example of panethnic screening involves cystic fibrosis when the American College of Obstetricians and Gynecologists (ACOG) noted that ethnic intermarriage was increasing in the U.S.[4,5,] and recommended panethnic cystic fibrosis carrier screening in 2005.[6,]

Non-targeted Carrier Screening

Non-targeted carrier screening involves screening individuals or couples for disorders in many genes (up to 100s) by next-generation sequencing. Non-targeted carrier screening 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. Arguments for non-targeted carrier screening include the potential to assess ethnicity, identify

more potential conditions, efficiency, and cost. The conditions included in non-targeted carrier screening panels are 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.

Carrier screening for mitochondrial disorders associated with autosomal recessive inheritance of nuclear DNA variants is addressed in this review. Diagnostic genetic testing for mitochondrial disorders and carrier testing of known familial variants associated with mitochondrial disorders are not addressed in this evidence review.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments 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 (ACOG, ACMG), to large non-targeted panels that test for numerous diseases.

POLICY

A. **Targeted Risk-Based Carrier Screening**

1. Targeted carrier screening for X-linked and autosomal recessive genetic diseases is considered **medically necessary** for individuals who are pregnant or are considering pregnancy and are at increased risk of having offspring with an X-linked or autosomal recessive disease when **ONE** of the following criteria is met:
   a. One or both individuals have a first- or second-degree relative who is affected; **OR**
   b. One individual is known to be a carrier; **OR**
   c. One or both individuals are members of a population known to have a carrier rate that exceeds a threshold considered appropriate for testing for a particular condition.

   AND ALL of the following criteria are met:

   d. The natural history of the disease is well understood and there is a reasonable likelihood that the disease is one with high morbidity or early mortality in the homozygous or compound heterozygous state (see Policy Guidelines);
   e. 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;
   f. The genetic test has adequate clinical validity to guide clinical decision-making and residual risk is understood;
   g. An association of the marker with the disorder has been established;
   h. If targeted testing is performed by a panel, the panel meets the minimum number of recommended gene variants but does not exceed the maximum, as determined by professional clinical guidelines (see Policy Guidelines). Non-targeted panels can be used instead of targeted testing when the criteria for non-targeted carrier screening are met (see below);
   i. Previous carrier screening or individual targeted gene testing for the gene variant(s) of interest has not been performed (see Policy Guidelines).

2. All targeted carrier screening not meeting any of the above criteria is considered **experimental / investigational**.

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

B. **Non-Targeted Carrier Screening**
   1. Non-targeted carrier screening panels for autosomal recessive and X-linked genetic disorders may be considered **medically necessary** as an alternative to testing of individual genes (eg, *SMN1* gene and *CFTR* gene) for individuals who are pregnant or are considering pregnancy at any risk level including high risk and average risk when **ALL** of the following criteria are met:
      a. The natural history of each disease is well understood and there is reasonable likelihood that the disease is one with high morbidity or early mortality in the homozygous or compound homozygous state (see Policy Guidelines);
      b. 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;
      c. The genetic test has adequate clinical validity to guide clinical decision-making and residual risk is understood;
      d. An association of the markers with the disorders has been established;
      e. If testing is performed by a panel, the panel meets the minimum number of recommended gene variants but does not exceed the maximum, as determined by professional clinical guidelines (see Policy Guidelines);
      f. Previous carrier screening has not been performed (see Policy Guidelines).

   2. Non-targeted carrier screening panels are considered **experimental / investigational** in all other situations when above criteria are not met (see Policy Guidelines).

POLICY GUIDELINES

See Appendix 1 for definitions and related genetic testing nomenclature. A list of higher volume tests and the associated laboratories with commonly associated CPT is provided in Appendix 2.

A. Carrier screening (targeted or non-targeted) is **only medically necessary once per lifetime**. Exceptions may be considered if advances in technology support medical necessity for retesting.

B. Targeted carrier screening for autosomal recessive or X-linked conditions is also called risk-based test or ethnic-based testing. If targeted testing is performed by a panel, the most appropriate panel code available should be used. The panel and the panel billing code should include *CFTR* and *SMN1.* If the carrier screening test is a panel less than 15 genes and does not include *CFTR* or *SMN1*, but would be 15 or more genes if including *CFTR* or *SMN1*, then it should be coded with 81443 (see Codes section). Panels closely resembling 81443 should be billed using 81443 rather than billing individually (ie, unbundling).

C. Non-targeted carrier screening applies to persons of any risk including average risk. Any panel using 81443 for non-targeted carrier screening must include the *CFTR* and *SMN1* genes. Non-targeted carrier screening panels should include the minimum number of genes but not exceed the maximum number of genes recommended by professional guidelines from the American College of Obstetricians and Gynecologists (ACOG;

2-22 conditions) or the American College of Medical Genetics and Genomics (ACMG; 113 genes).

D. The ACOG Committee Opinion 690 (reaffirmed in 2023) states that "Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening" and 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; PMID: 28225425]

E. The ACOG guideline includes a list of 22 conditions deemed reasonable to include in a carrier screening panel (see Appendix 2). While there is no agreed upon definition of severity across professional societies, these 22 conditions have severity that would be deemed profound or severe per publication based on previous work by ACMG and cited by the most recent ACMG guidelines.[Lazarin et al (2014); PMID: 25494330][Gregg et al (2021); PMID 34285390] All but one condition deemed reasonable by ACOG (alpha-thalassemia) would be classified as profound or severe based on collaborative clinical expert application of a trait-based algorithm; however, in this work it is not clear if the alpha-thalassemia genes *HBA1/HBA2* were classified based on hemoglobin Bart hydrops fetalis syndrome or hemoglobin H disease.[Arjunan et al (2020); PMID: 32474937] Carrier testing of autosomal recessive genes associated with severe disease with carrier frequency of greater than 1/100 is estimated to identify 82% of at-risk couples.[Guo et al (2019); PMID: 30846881]

F. In 2021, the ACMG recommended that the phrase "expanded carrier screening" be replaced by "carrier screening" as expanded carrier screening is not well or precisely defined by professional organizations.[Gregg et al (2021); PMID 34285390] Previously, 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 panethnic testing for cystic fibrosis).

G. The updated ACMG guideline now recommends a multi-tier approach to carrier screening for autosomal recessive and X-linked conditions, incorporating recommendations from the ACOG Committee Opinion 691 (2017),[ACOG Committee Opinion No. 691; PMID: 28225426] to enhance communication and precision while advancing equity in carrier screening (see Table PG1).[Gregg et al (2021); PMID 34285390] The consensus group recognized no accepted standard in defining the severity of various conditions; and, based on previously published work, use the following definitions: (1) profound: shortened lifespan during infancy or childhood, intellectual disability; (2) severe: death in early adulthood, impaired mobility or a [disabling] malformation involving an internal organ; (3) moderate: neurosensory

impairment, immune deficiency or cancer, mental illness, dysmorphic features; and (4) mild: not meeting one of those described.[Lazarin et al (2014); PMID: 25494330]

H. The ACMG consensus group recommends offering Tier 3 carrier screening (≥1/200 carrier frequency + Tier 2; see Table PG1) to all pregnant patients and those planning a pregnancy. Carrier testing of autosomal recessive genes associated with severe disease with carrier frequency greater than 1/100 is estimated to identify 82% of at-risk couples, and identify 93% of at-risk couples when testing for genes with greater than 1/200 carrier frequency.[Guo et al (2019); PMID: 30846881] The ACMG Tier 3 recommendations were based on estimates that moving from Tier 2 (≥1/100 carrier frequency) to Tier 3 (1/200 carrier frequency) provided additional identification of 4-9/10,000 at-risk couples depending on the endogamous population examined. When the population evaluated was weighted by U.S. census data, at-risk couples identified increased by 6 per 10,000 couples when moving from the Tier 2 (≥1/100) carrier frequency to that of Tier 3 (≥1/200). Assuming ~4 million births per year, this translates to an annual increase of identifying 2,400 additional U.S. couples.

I. The ACMG consensus group specified gene recommendations which include testing for 97 autosomal recessive genes and 16 X-linked genes, all of which associate with disorders of moderate, severe, or profound severity and are of 1/200 or greater carrier frequency. Non-targeted carrier screening panels that test for genes beyond this provide diminishingly small results, and pleiotropy, locus heterogeneity, variant interpretation, and poor genotype-phenotype correlation may disproportionately impact the ability to provide accurate prognostic information.[Gregg et al (2021); PMID 34285390]

J. Additionally, the recommendations include that male partners of pregnant women and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions when carrier screening is performed simultaneously with their female partner. Tier 4 screening may be offered when a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer) or when family or personal medical history warrants. The ACMG does not recommend offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups, or the routine offering of Tier 4 panels.

K. **Testing Strategy**

1. After testing the proband, targeted testing on the reproductive partner is preferred. Testing only applies to genes meeting criteria outlined above. If a lab does a more extensive test, then testing for other findings in the reproductive partner would not meet criteria. In general, carrier screening can be done once per lifetime. However, if only targeted or limited testing was done previously, then a more general non-targeted panel could be performed, particularly in cases where there is a new reproductive partner. In this case it is likely that genes could be re-tested.

Table PG1. American College of Medical Genetics and Genomics Tiered Approach to Carrier Screening[a]

Tier	Screening Recommendations
1	Cystic fibrosis + spinal muscular atrophy + risk-based screening
2	≥1/100 carrier frequency + Tier 1
3	≥1/200 carrier frequency + Tier 2 (includes X-linked conditions)
4	<1/200 carrier frequency + Tier 3 (genes and conditions will vary by laboratory)

ACMG: American College of Medical Genetics and Genomics
[a] Adapted from Gregg AR et al (2021; PMID 34285390).
X-linked genes considered appropriate for carrier screening in Tier 3 include: *ABCD1, AFF2, ARX, DMD, F8, F9, FMR1, GLA, L1CAM, MID1, NR0B1, OTC, PLP1, RPGR, RS1, and SLC6A8.* Refer to Tables 1 through 5 in the ACMG position statement for additional details regarding appropriate autosomal recessive conditions and their associated carrier frequencies. Additional details are available in the Supplemental Information section.
Carrier screening should only be performed in adults.

L. Genetic Counseling

1. 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.

M. Genetics Nomenclature Update

1. 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 PG2). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

2. The 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 PG3 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG2. 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 PG3. American College of Medical Genetics and Genomics-Association for Molecular Pathology Standards and Guidelines for Variant Classification

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

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 13, 2023.

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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 following PICO was used to inform literature selection.

Populations
The relevant population of interest are individuals or couples at risk for having offspring with inherited genetic 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 the 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 the 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.

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 American College of Obstetricians and Gynecologists (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.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). 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.[1,] 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 (eg, next-generation sequencing, microarray), clinical sensitivity and predictive values vary according to the proportion of known pathogenic variants evaluated. Clinical sensitivity will vary according to the number of known variants tested. Additionally, not all testing strategies rely solely on genetic testing-eg, 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 (eg, 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.

REVIEW OF EVIDENCE

Targeted Risk-Based Screening Recommendations

The ACOG and ACMG have issued numerous guidelines on targeted risk-based screening (see Table 1).

Table 1. American College of Obstetricians and Gynecologists and American College of Medical Genetics and Genomics Recommendations for Risk-Based Screening

Society	Recommendation	Year
Cystic fibrosis[a]		
ACOG	"Cystic fibrosis carrier screening should be offered to all women considering pregnancy or are pregnant."[7,]	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.[8,]	2013
Spinal muscular atrophy[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."[7,]	2017
ACMG	Because spinal muscular atrophy is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity.[9,]	2013
Tay-Sachs disease		
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"[7,]	2017
Fragile X syndrome		
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	2017

Society	Recommendation	Year
	hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an *FMR1* premutation."[7,]	

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.

The ACOG[7,] and the ACMG[10,] provided recommendations specific to individuals of Ashkenazi Jewish descent due to high carrier rates for multiple conditions in this population (see Table 2). According to ACMG, if only one 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 2. American College of Medical Genetics and Genomics (2008, 2013) and American College of Obstetricians and Gynecologists (2017) Carrier Screening Recommendations for Individuals of Ashkenazi Jewish Descent[7,10,]

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
Mucolipidosis IV	1/62,500	1/127	R	C
Gaucher disease	1/900	1/15	R	C
Familial hyperinsulinism		1/52		C
Glycogen storage disease type I		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.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Chain of Evidence
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.

Review of Evidence
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"[1,]). Evidence to support the clinical utility of carrier screening for conditions with the highest carrier rates (eg, Tay-Sachs disease, cystic fibrosis [CF]) among specific ethnic groups is robust concerning the effect on reproductive decision making.[3,11,12,13,] For example, early studies of Tay-Sachs carrier screening in Ashkenazi Jews demonstrated a marked impact on reproductive decisions[11,13,] and, after some 4 decades of ethnicity-based carrier screening, most Tay-Sachs disease cases occur in non-Jewish individuals.[12,] 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.[14,]Similarly, a 2023 systematic review that included studies of both targeted and non-targeted carrier screening found that carriers of conditions classified as having a more severe impact were more likely to terminate pregnancy or opt for in vitro fertilization with preimplantation genetic testing.[15,]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.[16,]

Section Summary: Targeted 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 the 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.

NON-TARGETED CARRIER SCREENING

Clinical Context and Test Purpose
The purpose of non-targeted carrier screening 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. Non-targeted 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 following PICO was used to inform literature selection.

Populations
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 non-targeted 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 non-targeted carrier screening.

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 the 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 the 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.

Study Selection Criteria
For the evaluation of the clinical utility of non-targeted carrier screening, 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 ACOG and ACMG consider risk-based carrier screening an established practice, guideline recommendations from these organizations will also be included in the evidence discussion.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). For conditions where pathogenic variants would be included in an non-targeted carrier screening (expanded carrier screening) panel, clinical validity should be demonstrated. Outside those targeted 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 the need for intervention.

ACOG (2017; reaffirmed 2023) made the following recommendations on expanded carrier screening[17,]:

"Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening"

Based on consensus, ACOG recommended the following criteria:

- carrier frequency ≥1/100;
- well-defined phenotype;
- detrimental effect on the 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, CF, 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.

In 2021, an updated position statement describing a multi-tier approach to carrier screening was published by ACMG.[18,] See Supplemental Information for additional details.

Review of Evidence

Many of the genes included in non-targeted carrier screening panels from different laboratories do not meet the prevalence criterion in all ethnic groups.[19,] However, self-reports of ethnicity may not be consistent with genetic ancestry in substantial proportion of individuals, particularly in countries with intermixed ethnicity such as the United States.[16,20,21,] A study by Guo and Gregg (2019) found that screening for the 40 genes that met the criterion of at least 1% prevalence in any ethnic group identified nearly all of the 2.52% of couples who would have been identified as at-risk.[22,]

Studies have been reported on larger non-targeted carrier screening panels (approximately 200 disorders) in the reproductive setting and are described in Tables 3 and 4. Terhaar et al (2018) compared positivity rates from 3 multi-gene carrier screening panels.[23,] Positivity rates increased with the number of genes tested, with 7.2% positivity for trio testing, 13.2% for a standard screen, and 35.8% for a global panel. Peyser et al (2019) reported that a non-targeted carrier screening panel identified 1243 carriers out of 4232 infertility patients (29.4%), while an ethnicity-based screen would have identified 359 (8.5%). The investigators calculated that out of the 1.2% of couples who carried the pathogenic variants for the same gene, 47% would have been missed with an ethnicity-based screen.[24,] In another study of patients who received non-targeted carrier screening at a fertility clinic, 1.7% of couples were at-risk for a recessive or X-linked disorder.[25,]

Several reports have been published on a commercially available 176 gene panel. The non-targeted carrier screening panel was designed for maximizing per-disease sensitivity for diseases categorized as severe or profound. Ben-Shachar et al (2019) considered all 176 conditions in a panel to meet ACOG criteria, except for the criterion of a carrier rate exceeding 1 in 100.[26,] In another analysis, medical geneticists evaluated disease severity associated with the 176 genes in

the panel.[27,] After evaluation of published literature and mapping according to ACOG severity criteria, the investigators concluded that 65 of the genes (36.9%) were associated with profound symptoms (shortened lifespan in infancy/childhood/adolescence and intellectual disability), 65 genes (36.9%) were associated with severe symptoms (shortened lifespan in infancy/childhood/adolescence or intellectual disability; or at least one of the following: shortened lifespan in premature adulthood, impaired mobility, internal physical manifestation with 3 or more traits: shortened lifespan in premature adulthood, impaired mobility, internal physical manifestation, sensory impairment, immunodeficiency/cancer, mental illness, or dysmorphic features), and 42 genes were associated with moderate symptoms. Moderate severity was classified as shortened lifespan in premature adulthood, impaired mobility, or internal physical manifestation; or, at least one of the following: sensory impairment, immunodeficiency/cancer, mental illness, or dysmorphic features. It is unclear if these would meet the ACOG criteria of a well-defined phenotype, a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life.

Other modeling studies have also estimated the incremental number of potentially affected fetuses if non-targeted carrier screening replaced a risk-based approach. Carrier rates with non-targeted carrier screening ranged from 19% to 36% in individuals and from 0.2% to 1.2% in couples. Westmeyer et al (2020) calculated that approximately 1 in 175 pregnancies would be affected by a disorder in a 274-gene screening panel.[21,] 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. The downstream impact similarly increases with a need for partner testing and genetic counseling.

Table 3. Relevant Clinical Validity Studies, Study Characteristics

Study	Setting	Study Design	Study Population	No. Screened	No. of Couples Screened	Disorders Screened
Terhaar et al (2018)[23,]	Referred for testing in a reproductive setting	Database review	51,584 samples analyzed with a trio panel 19,550 samples analyzed with a standard panel 3,902 samples analyzed with a global panel	75,036	NR	Trio panel = 3 Standard panel = 23 Global panel = 218
Peyser et al (2019)[24,]	Infertility clinic	Case series	All female and male patients who did not opt out	4232	1206	100
Hernandez-Nieto et al (2020)[25,]	Infertility clinics in Mexico and U.S.	Case series	Patients undergoing fertility treatments	805	391	283

Study	Setting	Study Design	Study Population	No. Screened	No. of Couples Screened	Disorders Screened
			were offered genetic testing.			

NR: not reported.
[a] By obstetricians, family practitioners, geneticists, genetics counselors, perinatologists, and reproductive endocrinologists.

Table 4. Relevant Clinical Validity Studies, Results

Study	Individual Carriers, n (%)[a]	Couple Carriers, n (%)	Incremental Findings Over Risk-Based Testing N (95% CI)	Incremental Findings Over ACOG Recommended Screen
Terhaar et al (2018)[23,]	(35.8%)	NA	35.8% vs. 7.2% for trio panel	35.8% vs. 13.2% for a 23 gene panel
Peyser et al (2019)[24,]	1243 (29.4%)	15 (1.2%)	884	584
Hernandez-Nieto et al (2020)[25,]	352 (43.7%)	17 (4.34%) 1.7% for X-linked or recessive disorders	NR	NR

ACOG: American College of Obstetricians and Gynecologists; CI: confidence interval; NA: not applicable; NR: not reported.
[a] One or more disorders.

Subsection Summary: Clinical Validity

Studies have found that non-targeted carrier screening identifies more carriers and potentially affected fetuses. Many of the genes in non-targeted carrier screening do not meet the ACOG consensus-driven criteria of at least 1% carrier rate for all ethnic groups. However, panethnic testing has also been supported by ACOG, which may address the discrepancies between self-reported ethnicity and genetic ancestry, particularly in ethnically mixed populations such as the U.S. One study calculated that a panethnic panel of 40 genes with at least a 1% prevalence in any ethnicity would address nearly all of the at-risk couples. As panels become larger, the likelihood of being identified as a carrier of a rare genetic disorder increases, resulting in an at-risk couple rate of nearly 2% for a recessive or X-linked disorder. Many, though not all, of these rare genetic disorders are associated with severe or profound symptoms including shortened lifespan and intellectual or physical disability.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. 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
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. A chain of evidence that non-targeted carrier screening offers greater clinical utility than recommended risk-based approaches, relies on clinical validity - a well-defined predictable risk that the offspring will be affected by severe phenotype - to non-targeted carrier screening and should correctly identify more carrier couples of severe phenotype conditions than recommended risk-based screening.

As noted in the section above, a 2023 systematic review that included studies of both targeted and non-targeted carrier screening found that carriers of conditions classified as having a more severe impact were more likely to terminate pregnancy or opt for in vitro fertilization with preimplantation genetic testing.[15,]

Several survey studies evaluated patients' perspectives and reproductive behaviors specifically concerning non-targeted carrier screening (see Table 5 and 6). For couples in which both partners carried genes for the same recessive disorder, actions following non-targeted carrier screening were reported in 60% to 91% of couples; the exact percentage depended upon the severity of disease. Frequently reported actions are prenatal screening or in vitro fertilization with preimplantation genetic diagnosis.

Clinical utility is supported by studies noted in the section above on ethnicity-based carrier testing, for which there is strong evidence of the impact of carrier screening on reproductive decision making and its effect on the prevalence of severe recessive disorders.[3,11,12,13,] For non-targeted carrier screening, a modeling study of the 176 gene panel described above found that compared with testing just for CF and spinal muscular atrophy, there would be a clinical impact on lifetime costs and life-years lost for 290 out of 100,000 pregnancies.[28,]

Table 5. Characteristics of Observational Studies for Clinical Utility

Author (Year)	Study Type	Country	Dates	Participants	Number	Outcomes
Ghiossi et al (2018)[29,]	Retrospective survey	United States	2014 to 2015	Couples in which both partners carry genes for the same recessive disease (profound, severe, or moderate per Lazarin et al. 2014) who had received ECS	537 eligible couples,64 (12%) completed survey	• Action (defined as IVF with PGD or prenatal diagnosis) • No action

Author (Year)	Study Type	Country	Dates	Participants	Number	Outcomes
Johansen Taber et al (2018)[30,]	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 (ie, non-targeted) carrier screening; IVF: in vitro fertilization; NR: not reported; PGD: preimplantation genetic diagnosis.

Table 6. Results of Observational Studies for Clinical Utility

Study (Year)	Results
Ghiossi et al (2018)[29,]	• 60% reported taking action (IVF with PGD or prenatal diagnosis) following ECS results. • 40% reported taking no action following ECS results. • Of at-risk couples carrying severe or profound conditions, 76% (32/42) reported alternative reproductive actions, versus 22% (4/18) at-risk couples carrying moderate conditions suggesting that disease severity has a significant effect on reproductive actions (p=.000145).
Johansen Taber et al (2018)[30,]	• 77% of patients screened before becoming pregnant planned or pursued actions to avoid having affected offspring (91% for a profound condition, 77% for a severe condition, and 65% for a moderate condition). • 37% of patients screened during pregnancy pursued prenatal diagnostic testing (49% if excluding those reporting they underwent IVF with pre-implantation genetic testing, those who reported testing performed too late to allow termination, and those reporting termination had occurred before test results returned), of which 8 affected pregnancies were terminated (1/8 for moderate disorders and 7/8 for severe or profound disorders). • Reasons for declining prenatal testing were fear of miscarriage, belief that termination would not be pursued in the event of a positive diagnosis or perception that the risk of an affected pregnancy was low.

ECS: expanded (ie, non-targeted) carrier screening; IVF: in vitro fertilization; PGD: preimplantation genetic diagnosis.

Section Summary: Expanded Carrier Screening

Indirect evidence on clinical utility depends on the demonstration that the genes included in non-targeted carrier screening are associated with severe genetic disorders, as described in the section above on clinical validity. The clinical utility of non-targeted carrier screening is the ability to affect reproductive choices such as in vitro fertilization with preimplantation genetic diagnosis or prenatal genetic testing to avoid a severe genetic disorder in the offspring. Observational studies have shown that a majority of couples would consider intervention, with a percentage choosing intervention that depends on the severity of the condition. Modeling suggests that the clinical impact of avoiding severe genetic disorders, even if rare, is high.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists
In 2017 (reaffirmed in 2023), the American College of Obstetricians and Gynecologists (ACOG) made the following recommendations on expanded (ie, non-targeted) carrier screening [17,]:

"Ethnic-specific, panethnic, 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 the 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.

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

In 2015, a joint statement on expanded carrier screening was issued by ACOG, the American College of Medical Genetics and Genomics (ACMG), the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine.[2,] The statement was not intended to replace current screening guidelines but to demonstrate an approach for healthcare providers and laboratories seeking to or currently offering expanded carrier screening panels. Some points considered included the following.

"Expanded carrier screening panels include most of the conditions recommended in current guidelines. However, molecular methods used in expanded carrier screening are not as accurate as methods recommended in current guidelines for the following conditions:
- Screening for hemoglobinopathies requires use of mean corpuscular volume and hemoglobin electrophoresis.
- Tay-Sachs disease carrier testing has a low detection rate in non-Ashkenazi populations using molecular testing for the 3 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 expanded carrier screening. 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."

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

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

American College of Medical Genetics and Genomics

In 2021, the ACMG issued a position statement on screening for autosomal recessive and X-linked conditions during pregnancy and preconception.[18,] This position statement replaces the 2013 ACMG position statement on prenatal and preconception expanded carrier testing, and incorporates ACOG Committee Opinion 691 recommendations.[7,]

The ACMG consensus group made the following recommendations:

- Replacing the term "expanded carrier screening" with "carrier screening" as no precise definition for "expanded" exists.
- Establishing a tier-based system of carrier screening, to enhance communication and precision while advancing equity in carrier screening (see Table 7 below).
- Carrier screening paradigms should be ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion.
- Offering Tier 3 carrier screening to all pregnant patients and those planning a pregnancy.
- Male partners of pregnant women and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions when carrier screening is performed simultaneously with their female partner.
- Consider offering Tier 4 screening when a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer) or when family or personal medical history warrants.

The ACMG does not recommend:

- Offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups.
- Routine offering of Tier 4 panels.

Table 7. American College of Medical Genetics and Genomics Tiered Approach to Carrier Screening[18,]

Tier	Screening Recommendations
1	Cystic fibrosis + spinal muscular atrophy + risk based screening
2	≥1/100 carrier frequency + Tier 1
3	≥1/200 carrier frequency + Tier 2 (includes X-linked conditions)
4	<1/200 carrier frequency + Tier 3 (genes and conditions will vary by lab)

ACMG: American College of Medical Genetics and Genomics

X-linked genes considered appropriate for carrier screening in Tier 3 include: *ABCD1, AFF2, ARX, DMD, F8, F9, FMR1, GLA, L1CAM, MID1, NR0B1, OTC, PLP1, RPGR, RS1, and SLC6A8.* Refer to Tables 1 through 5 in the ACMG position statement for additional details regarding appropriate autosomal recessive conditions for screening and their associated carrier frequencies.

The ACMG recommends the following components regarding laboratory reporting of carrier screening panels:

- The content of carrier screen panels and corresponding ACMG tier must be described.
- The testing approach and detectable variant types should be clearly stated.
- Not reporting residual risk estimates.
- Only reporting pathogenic and likely pathogenic variants.
- Interpretation should consider genes and variants with multiple disease associations.
- Reporting of a variant of uncertain significance (VUS) only in the partners of identified carriers and only with consent of the patient.

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.

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04157595	Mackenzie's Mission: The Australian Reproductive Carrier Screening Project	18,302	Dec 2023 (ongoing)
Unpublished			
NCT01902901	Clinical Implementation of Carrier Status Using Next Generation Sequencing	384	May 2018

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
0400U	Obstetrics (expanded carrier screening), 145 genes by next generation sequencing, fragment analysis and multiplex ligation dependent probe amplification, DNA, reported as carrier positive or negative

REVISIONS	
Posted 12-01-2023 Effective 01-01-2024	Policy added to the bcbsks.com web site.

REFERENCES

1. Henneman L, Borry P, Chokoshvili D, et al. Responsible implementation of expanded carrier screening. Eur J Hum Genet. Jun 2016; 24(6): e1-e12. PMID 26980105
2. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. Mar 2015; 125(3): 653-662. PMID 25730230
3. Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. Eur J Pediatr. Dec 2000; 159 Suppl 3: S192-5. PMID 11216898

4. Banda Y, Kvale MN, Hoffmann TJ, et al. Characterizing Race/Ethnicity and Genetic Ancestry for 100,000 Subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort. Genetics. Aug 2015; 200(4): 1285-95. PMID 26092716
5. Grant MD, Lauderdale DS. Cohort effects in a genetically determined trait: eye colour among US whites. Ann Hum Biol. 2002; 29(6): 657-66. PMID 12573082
6. Committee on Genetics, American College of Obstetricians and Gynecologists. ACOG Committee Opinion. Number 325, December 2005. Update on carrier screening for cystic fibrosis. Obstet Gynecol. Dec 2005; 106(6): 1465-8. PMID 16319281
7. Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. Mar 2017; 129(3): e41-e55. PMID 28225426
8. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. 2004; 6(5): 387-91. PMID 15371902
9. Prior TW. Carrier screening for spinal muscular atrophy. Genet Med. Nov 2008; 10(11): 840-2. PMID 18941424
10. Gross SJ, Pletcher BA, Monaghan KG. Carrier screening in individuals of Ashkenazi Jewish descent. Genet Med. Jan 2008; 10(1): 54-6. PMID 18197057
11. Burke W, Tarini B, Press NA, et al. Genetic screening. Epidemiol Rev. 2011; 33(1): 148-64. PMID 21709145
12. Bajaj K, Gross SJ. Carrier screening: past, present, and future. J Clin Med. Sept 2015 2014;3(3):1033-1042. PMC4449659
13. Kaback M, Lim-Steele J, Dabholkar D, et al. Tay-Sachs disease--carrier screening, prenatal diagnosis, and the molecular era. An international perspective, 1970 to 1993. The International TSD Data Collection Network. JAMA. Nov 17 1993; 270(19): 2307-15. PMID 8230592
14. Ioannou L, McClaren BJ, Massie J, et al. Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. Genet Med. Mar 2014; 16(3): 207-16. PMID 24030436
15. Wang T, Kiss D, McFadden K, et al. Clinical utility of reproductive carrier screening for preconception and pregnant couples for multiple genetic conditions: a systematic review and meta-analysis. Expert Rev Mol Diagn. May 2023; 23(5): 419-429. PMID 37086152
16. Shraga R, Yarnall S, Elango S, et al. Evaluating genetic ancestry and self-reported ethnicity in the context of carrier screening. BMC Genet. Nov 28 2017; 18(1): 99. PMID 29179688
17. Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. Obstet Gynecol. Mar 2017; 129(3): e35-e40. PMID 28225425
18. Gregg AR, Aarabi M, Klugman S, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. Oct 2021; 23(10): 1793-1806. PMID 34285390
19. Stevens B, Krstic N, Jones M, et al. Finding Middle Ground in Constructing a Clinically Useful Expanded Carrier Screening Panel. Obstet Gynecol. Aug 2017; 130(2): 279-284. PMID 28697118
20. Kaseniit KE, Haque IS, Goldberg JD, et al. Genetic ancestry analysis on 93,000 individuals undergoing expanded carrier screening reveals limitations of ethnicity-based medical guidelines. Genet Med. Oct 2020; 22(10): 1694-1702. PMID 32595206

21. Westemeyer M, Saucier J, Wallace J, et al. Clinical experience with carrier screening in a general population: support for a comprehensive pan-ethnic approach. Genet Med. Aug 2020; 22(8): 1320-1328. PMID 32366966
22. Guo MH, Gregg AR. Estimating yields of prenatal carrier screening and implications for design of expanded carrier screening panels. Genet Med. Sep 2019; 21(9): 1940-1947. PMID 30846881
23. Terhaar C, Teed N, Allen R, et al. Clinical experience with multigene carrier panels in the reproductive setting. Prenat Diagn. Apr 23 2018; 38(8): 572-7. PMID 29683194
24. Peyser A, Singer T, Mullin C, et al. Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates. Genet Med. Jun 2019; 21(6): 1400-1406. PMID 30327537
25. Hernandez-Nieto C, Alkon-Meadows T, Lee J, et al. Expanded carrier screening for preconception reproductive risk assessment: Prevalence of carrier status in a Mexican population. Prenat Diagn. Apr 2020; 40(5): 635-643. PMID 32003480
26. Ben-Shachar R, Svenson A, Goldberg JD, et al. A data-driven evaluation of the size and content of expanded carrier screening panels. Genet Med. Sep 2019; 21(9): 1931-1939. PMID 30816298
27. Arjunan A, Bellerose H, Torres R, et al. Evaluation and classification of severity for 176 genes on an expanded carrier screening panel. Prenat Diagn. Sep 2020; 40(10): 1246-1257. PMID 32474937
28. Beauchamp KA, Johansen Taber KA, Muzzey D. Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen. Genet Med. Sep 2019; 21(9): 1948-1957. PMID 30760891
29. Ghiossi CE, Goldberg JD, Haque IS, et al. Clinical Utility of Expanded Carrier Screening: Reproductive Behaviors of At-Risk Couples. J Genet Couns. Jun 2018; 27(3): 616-625. PMID 28956228
30. Johansen Taber KA, Beauchamp KA, Lazarin GA, et al. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet Med. May 2019; 21(5): 1041-1048. PMID 30310157

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 one abnormal allele for a disorder. When associated with an autosomal recessive or X-linked disorder, carriers of the causative variant are typically unaffected. When associated with an autosomal dominant disorder, the individual has one normal and one mutated copy of the gene and may be affected 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 (eg, if the individual carries a pathogenic variant not included in the test assay).

Appendix 2. Resources
A list of selected higher volume tests and associated laboratories, CPT, and ICD-10 codes is provided below in Appendix Table 1.

Appendix Table 1. Common Carrier Screening Tests

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD-10 Codes
Expanded Carrier Screening Panels	Foresight, Myriad Horizon, Natera Inheritest, LabCorp Preparent Standard/Global, Progenity GeneSeq, LabCorp	81443	O09, Z13, Z31, Z34, Z36, Z84
α-Thalassemia Carrier Screening	HBA1 Sequencing HBA2 Sequencing	81257, 81258, 81259, 81269	Z31
Ashkenazi Jewish Carrier Panel Testing	Foresight: AJ Panel, Counsyl Inheritest: AJ Panel, LabCorp Horizon 106 (Comprehensive Jewish Panel), Natera	81412	O09, Z13, Z31, Z34, Z36, Z84
Cystic Fibrosis Carrier Screening	CFTR Common Mutation Panel	81220	O09, Z13, Z31, Z34, Z36, Z84
Duchenne and Becker Muscular Dystrophy Carrier Screening	DMD Deletion/Duplication Analysis	81161	Z31
Fragile X Syndrome Carrier Screening	FMR1 Repeat Analysis	81243, 81244	O09, Z13, Z31, Z34, Z36, Z84
Hereditary Hearing Loss Carrier Screening	GJB2 Sequencing GJB6 Sequencing	81252, 81253, 81254, 81430, 81431, S3844	O09, Z13, Z31, Z84
Mitochondrial Disorder Carrier Screening	MT-TL1 Targeted Mutation Analysis, Mitochondrial DNA Point Mutations and Deletions Screening Panel	81401, 81403, 81404, 81405, 81406, 81445, 81460, 81465	E88.4, O09, Z13, Z31, Z84
Spinal Muscular Atrophy Carrier Screening	SMN1 Deletion/Duplication Analysis SMN2 Deletion/Duplication Analysis	81329, 81336, 81337	O09, Z13, Z31, Z34, Z36, Z84
Tay-Sachs Carrier Screening	HEXA Targeted Mutation Analysis	81255	O09, Z13, Z31, Z34, Z36, Z84
General Criteria for Targeted Carrier Testing			O09, Z13, Z31, Z34, Z36, Z84

A list of 22 conditions deemed reasonable to include in a carrier screening panel were published by ACOG in Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine.[17,] These conditions are summarized below in Appendix Table 2.

Appendix Table 2. Example of an Expanded Carrier Screening Panel (ACOG 2017; Reaffirmed 2020)[a]

Condition	Carrier Frequency in General Population	Carrier Frequency in Specific Ethnic Groups
α-thalassemia	Unknown	African (particularly sub-Saharan): 1 in 3 Mediterranean: 1 in 30 Southeast Asian and Middle Eastern: 1 in 20
β-thalassemia	Unknown	African American: <1 in 8 Ashkenazi Jewish: Varied Asian: 1 in 20 Mediterranean: 1 in 7
Bloom syndrome	<1 in 500	Ashkenazi Jewish: 1 in 100
Canavan disease	<1 in 150	Ashkenazi Jewish: 1 in 41
Cystic fibrosis	Unknown	African American: 1 in 61 Asian: 1 in 94 Ashkenazi Jewish: 1 in 24 Caucasian: 1 in 25 Hispanic: 1 in 58
Familial dysautonomia	<1 in 500	Ashkenazi Jewish: 1 in 31
Familial hyperinsulinism	<1 in 150	Ashkenazi Jewish: 1 in 52
Fanconi anemia C	<1 in 790	Ashkenazi Jewish: 1 in 89
Fragile X syndrome[b]	1 in 259	
Galactosemia	1 in 87	Ashkenazi Jewish: 1 in 127
Gaucher disease	<1 in 100	Ashkenazi Jewish: 1 in 15
Glycogen storage disease type 1A	<1 in 150	Ashkenazi Jewish: 1 in 71
Joubert syndrome	<1 in 500	Ashkenazi Jewish: 1 in 92
Medium-chain acyl-CoA dehydrogenase deficiency	Unknown	Caucasian: 1 in 50
Maple syrup urine disease types 1A and 1B	1 in 240	Ashkenazi Jewish: 1 in 81 (type 1B) Mennonite: 1 in 10 (type 1A-*BCKDHA* p.Y438N)
Mucolipidosis IV	<1 in 500	Ashkenazi Jewish: 1 in 96
Niemann-Pick disease type A	<1 in 500	Ashkenazi Jewish: 1 in 90
Phenylketonuria	Unknown	Caucasian: 1 in 50 Irish: 1 in 34
Sickle cell anemia	Unknown	African American: 1 in 10
Smith-Lemli-Opitz syndrome	Unknown	Caucasian: 1 in 70

Condition	Carrier Frequency in General Population	Carrier Frequency in Specific Ethnic Groups
Spinal muscular atrophy	Unknown	African American: 1 in 66 Asian: 1 in 53 Ashkenazi Jewish: 1 in 41 Caucasian: 1 in 35 Hispanic: 1 in 117
Tay-Sachs disease[c]	1 in 300	Ashkenazi Jewish: 1 in 30 French Canadian and Cajun: 1 in 30

ACOG: American College of Obstetricians and Gynecologists.
[a] Adapted from ACOG Committee Opinion 690.[17,]
[b] Recommended despite a carrier frequency lower than 1 in 100 because fragile X syndrome is more prevalent than other X-linked syndromes.
[c] DNA testing alone will miss up to 10% of carriers, especially in low risk groups. Therefore, enzyme-based testing may be a more appropriate choice for some patients.