Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Genetic Testing - Carrier Screening for Genetic Diseases

Description/Background

NOTE: This evidence review applies only if there is not a separate Joint Uniform Medical Policy (JUMP) that outlines specific criteria for testing of a specific gene as targeted carrier testing. If a separate JUMP policy exists, then criteria for medical necessity in that policy supersede the guidelines in this policy.

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.

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 is testing 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 "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 pan-ethnic. An example of effective ethnicity-based screening involves Tay-Sachs disease, with a 90% reduction in the disease following the introduction of carrier screening in the 1970s in the United States and Canada.(3) An example of pan-ethnic screening involves cystic fibrosis, when the American College of Obstetricians and Gynecologists noted that ethnic intermarriage was

increasing in the U.S.(4,5) and recommended pan-ethnic 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 (NGS). 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 panels 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.

American College of Medical Genetics and Genomics (ACMG – 2021) released updated recommendations that panethnic panels (non-targeted carrier screening panels) be available to all for some autosomal recessive and x-linked genetic diseases. One-hundred and thirteen genes were identified and categorized into tiers with recommendations on how to use the new tiered system.

DEFINITIONS

Carrier Testing
Carrier genetic testing is performed on people who display no symptoms for a genetic disorder but may be at risk for passing it on to their children.

A carrier of a genetic disorder has one abnormal allele for a disorder. When associated with an autosomal recessive or X-linked disorder, carriers of the causative genetic variant are typically unaffected. When associated with an autosomal dominant disorder, the individual has one normal and one variant of the gene and may be affected with 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 genetic variant from both parents) manifest the disorder.

Compound Heterozygous
The presence of two different abnormal 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 non-inherited (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 genetic variant that causes a particular disorder who exhibit clinical symptoms of that disorder.

Residual Risk
The risk that an individual is a carrier of a particular disease, but genetic testing for carrier status of the disease is negative (e.g., if the individual has a disease-causing variant that wasn't included in the test assay).

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 the 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 as recommended by practice guidelines (American College of Medical Genetics and Genomics), to large, non-targeted panels that test for numerous diseases.

The following is a list of some of the available panels, but it is not comprehensive.

Counsyl™ (Counsyl) tests for more than 100 diseases, which, according to the manufacturer website, lead to shortened lifespan, have limited treatment or can lead to intellectual disability. Diseases tested for include those recommended by ACOG, ACMG, as well as an Ashkenazi Jewish panel, fragile X syndrome, a 100-mutation CF panel, sickle cell disease, and metabolic disorders.

GoodStart Select™ (GoodStart Genetics) "customizes" the testing panel for each patient based on ethnicity, family history, and provider testing preferences. The test menu includes several ethnic panels, and includes testing for hemoglobinopathies, fragile X syndrome, CF, metabolic disorders, and others.

Inherigen™ (GenPath) is a pan-ethnic test for over 160 inherited disorders, typically those with childhood onset and severe symptoms, such as immunodeficiencies and several metabolic diseases, such as Tay-Sachs disease, glycogen storage diseases, and fatty acid oxidation disorders. InheriGen Plus includes all InheriGen diseases plus CF, SMA, and fragile X syndrome.

Inheritest™ (LabCorp) is a pan-ethnic test for more than 90 autosomal recessive inherited diseases. The Inheritest Select Carrier Screen is a test that evaluates diseases for patients of Ashkenazi Jewish descent.

Natera One™ Disease Panel (Natera) tests for 13 diseases, which include ACMG-recommended tests for carrier screening, plus fragile X syndrome, sickle cell anemia, hemoglobin C trait, and SMA.

Natera Horizon have five different panels that screen for as few as four and up to 274 autosomal and X-linked genetic conditions. The panels are pan-ethnic, ancestry-based, or non-targeted.

UNITY Carrier Screen™, BillionToOne Laboratory, BillionToOne, Inc. Carrier screening for severe inherited conditions (e.g., cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2)

Two CLIA-certified laboratories, Progenity™ (Ann Arbor, Michigan; formerly aMDx Laboratory Sciences and Ascendant MDx) and Sequenom® Laboratories (San Diego, CA), offer single disease carrier testing (cystic fibrosis [CFnxt cystic fibrosis and HerediT™ Cystic Fibrosis Carrier Screen, respectively], fragile X syndrome [Fragile X syndrome and HerediT™ Cystic Fibrosis Carrier Screen, respectively], SMA [SMAnxt spinal muscular atrophy and HerediT™ Spinal Muscular Atrophy Carrier Screen, respectively]) and disease panels for Ashkenazi Jewish patients (AJPnxt Basic [9 diseases] or AJPnxt Expanded [19 diseases] and HerediT™ Ashkenazi Jewish Panel Carrier Screen [17 diseases], respectively). Progenity™ also offers nxtPanel for simultaneous CF, SMA, and fragile X syndrome testing.

Medical Policy Statement

Non-targeted carrier screening (panel testing) for autosomal recessive and x-linked genetic disorders have been established. It may be considered a useful diagnostic option when indicated.

The safety and effectiveness of targeted carrier screening for autosomal recessive and x-linked genetic disorders have been established. It may be considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:

Non-Targeted Carrier Screening

- Testing of the female partner for autosomal recessive and x-linked genetic disorders when the female is pregnant or is considering pregnancy. (This is often performed as panel testing)*
- Testing should include screening for spinal muscular atrophy (SMN1 gene) and cystic fibrosis (CFTR).
- If the initial testing of the female is positive, then testing in the male partner should be focused on that/those specific gene abnormality(ies).

- This testing is only medically necessary once per lifetime. Exceptions may be considered if advances in technology support medical necessity for retesting.

* The ACMG 113 recommended genes are listed in Tables 8-10 on pages 20-24 of this policy

Targeted Risk Based Carrier Screening
This screening is for autosomal recessive and x-linked genetic disorders when the following apply:

- The couple is pregnant or is considering pregnancy and **one** of the following are met:
  - One individual is known to be a carrier
  - One or both individuals have a first- or second-degree relative who is affected
    - First degree includes biological: parent, sibling, and child
    - Second degree includes biological: grandparent, aunt, uncle, niece, nephew, grandchildren and half-sibling
  - 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 (**applies to targeted screening**):

- 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 sensitivity and specificity to guide clinical decision making and residual risk is understood.
- An association of the marker with the disorder has been established.

Exclusions:

- All targeted and non-targeted carrier screening panels not meeting the above criteria
- Carrier screening of the male partner when the female partner was found not to have risk (i.e., sequential testing)
- Carrier screening of the male partner at the same time that the female partner is undergoing carrier screening (i.e., simultaneous testing)
- If previous non-targeted carrier screening **or** individual targeted gene testing for the gene(s) of interest have been performed, then repeat screening is not approved

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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

*Various codes	81412	81443

**Tier 1 or Tier 2 as indicated. If the test has not been codified by CPT, the unlisted molecular pathology code 81479 would be used.*

Panels closely resembling 81443 should be billed using 81443 rather than billing individually (i.e., unbundling).

Other codes (investigational, not medically necessary, etc.):

0400U 0449U

Policy Guidelines

Emphasis is placed on the consent process including elements of pre- and post-test counseling as described by the American College of Medical Genetics and Genomics.

The ACOG Committee Opinion 690 (reaffirmed in 2023) states that "Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy 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."(1)

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.(3) 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 (e.g., ethnic-specific screening or panethnic testing for cystic fibrosis).

The updated ACMG guideline now recommends a multi-tier approach to carrier screening for autosomal recessive and X-linked conditions(3) incorporating recommendations from the ACOG Committee Opinion 691 (2017),(6) to enhance communication and precision while advancing equity in carrier screening (see Table PG1).(3) 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.

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.(5) 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.

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.(3)

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.

Testing Strategy

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 (3)

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

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 in the ACMG position statement for additional details regarding appropriate autosomal recessive conditions and their associated carrier frequencies. Available in the Supplemental Information section.

Carrier screening should only be performed in adults.

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 those who meet criteria for testing.

Rationale

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 PICOs were used to inform literature selection.

Populations

The relevant populations 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 Ashkenazi panel.

Comparators

The comparator of interest is no carrier screening.

Outcomes

The primary outcome of interest is reproductive decision making.

A beneficial outcome of a true test result is an informed reproductive decision 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 (e.g., 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—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.

Review of Evidence

Targeted Risk-Based Screening Recommendations

The American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics and Genomics (ACMG) have issued numerous guidelines on targeted risk-based screening (see Table 1).

Table 1. ACOG and ACMG 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."	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.	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."	2017
ACMG	Because spinal muscular atrophy is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity.	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"	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 hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an FMR1 premutation."	2017

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 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. ACMG (2008, 2013) and ACOG (2017) Carrier Screening Recommendations for Individuals of Ashkenazi Jewish Descent

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	1/62,5000	1/127	R	C
Gaucher disease	1/900	1/15	R	C
Familial hyperinsulinism		1/52		C
Glycoden 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 (i.e., increases "reproductive autonomy and choice").(1) Evidence to support the clinical utility of carrier screening for conditions with the highest carrier rates (e.g., Tay-Sachs disease, cystic fibrosis [CF]) among specific ethnic groups is robust concerning the effect on reproductive decision making.(3,11-13) For example, early studies of Tay-Sachs carrier screening in Ashkenazi Jews demonstrated a marked impact on reproductive decisions (11,13) and, after some four decades of ethnicity-based carrier screening, most Tay-Sachs disease cases occur in non-Jewish individuals.(17) 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.

NONTARGETED CARRIER SCREENING

Clinical Context and Test Purpose

The purpose of nontargeted 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 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 PICOs were 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 using 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 the ACOG and the American College of Medical Genetics and Genomics (ACMG) consider risk-based carrier screening an established practice, guideline recommendations from these organizations will also be included in the evidence discussion.

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 a carrier screening panel, clinical validity should be demonstrated. Outside those defined variants, pathogenicity, penetrance, and expressivity together with disease severity require accurate definition. Subsumed in clinical validity is the effect of a condition's severity on quality of life, impairments, and the need for intervention.

ACOG (2017; reaffirmed 2023) made the following recommendations on expanded carrier screening (ECS):(17)
- "Ethnic-specific, panethnic, and carrier screening panels are acceptable for pre-pregnancy and prenatal carrier screening."

Based on consensus, ACOG recommend 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, cystic fibrosis, familial dysautonomia, familial hyperinsulinism, Fanconi anemia C, fragile X syndrome, galactosemia, Gaucher disease, glycogen storage disease type 1A, Joubert syndrome, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease types 1A and 1B, mucolipidosis IV, Niemann-Pick disease type A, phenylketonuria, sickle cell anemia, Smith-Lemli-Opitz syndrome, spinal muscular atrophy, and Tay-Sachs disease.

In 2021, an updated position statement describing a multi-tier approach to carrier screening was published by ACMG.(18) See Supplemental section 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 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 a 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 non-targeted 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)	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 = 3 Standard = 23 Global = 218
Peyser et al (2019)	Infertility clinic	Case series	All female and male patients who did not opt out	4232	1206	100
Hernandez-Nieto et al (2020)	Infertility clinics in Mexico and U.S.	Case series	Patients undergoing fertility treatments were offered genetic testing.	805	391	283

NR: not reported.

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)	(35.8%)	NA	35.8% vs 7.2% for trio	35.8% vs 13.2% for a 23 gene panel
Peyser et al (2019)	1243 (29.4%)	15 (1.2)	884	584
Hernandez-Nieto et al (2020)	352 (43.7%)	17 (4.34%) 1.7% for X-linked or recessive disorders	NR	NR

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

Section 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, pan-ethnic 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 pan-ethnic 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 both 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 surveys 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.(3,11-13) For non-targeted carrier screening, a modeling study of the 176 gene panel described above found

that compared with testing just for cystic fibrosis 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)	Retrospective survey	United States	2014 to 2015	Couples in which both partners carry genes for the same recessive disease who had received ECS	537 eligible couples 64 (12%) completed survey	• Action (defined as IVF with PGD or prenatal diagnosis) • No action
Johansen Taber et al (2018)	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 (i.e., non-targeted carrier screening; IVF: invitro fertilization; NR: not reported; PGD: preimplantation genetic diagnosis

Table 6. Results of Observational Studies for Clinical Utility

Study (Year)	Results
Ghiossi et al (2018)	• 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 (ARC) carrying severe or profound conditions, 76% (32/42) reported alternative reproductive actions, versus 22% (4/18) ARC carrying moderate conditions suggesting that disease severity has a significant effect on reproductive actions (p =.000145)
Johansen Taber et al (2018)	• 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 (i.e., non-targeted) carrier screening; IVF: invitro fertilization; PGD: preimplantation genetic diagnosis

Section Summary: Non-Targeted 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.

SUMMARY OF EVIDENCE

For individuals who are asymptomatic but at risk for having offspring with an inherited x-linked or autosomal recessive genetic disorder who receive targeted risk-based carrier screening, the evidence includes studies supporting clinical validity, and clinical utility. Relevant outcomes are test validity, and changes in reproductive decision making. Results of carrier testing can be used to inform reproductive decisions such as preimplantation genetic diagnosis, in vitro fertilization, not having a child, invasive prenatal testing, adoption, or pregnancy termination. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are either at increased risk or population risk for having offspring with an inherited x-linked or autosomal recessive genetic disorder who receive testing with a non-targeted carrier screening panel, the evidence includes studies supporting clinical validity, and clinical utility. Relevant outcomes are test validity, and changes in reproductive decision making. Studies have found that non-targeted carrier screening identifies more carriers and more potentially affected fetuses. Many of the genes in carrier screening panels do not meet the ACOG consensus-driven criteria of at least 1% carrier rate for all ethnic groups. However, non-targeted testing can address the discrepancies between self-reported ethnicity and genetic ancestry in an ethnically mixed population. As panels become larger the likelihood of being identified as a carrier of a rare genetic disorder increases, leading to an at-risk couple rate of nearly 2% for having an offspring with a recessive or X-linked disorder. Many, though notably not all, of these rare genetic disorders are associated with severe or profound symptoms including shortened lifespan and intellectual or physical disability. With adequate genetic counseling carrier screening panels can inform reproductive choices, and observational studies have shown that a majority of couples would consider intervention that depends on the severity of the condition. Therefore, non-targeted carrier screening panels for severe recessive and X-linked genetic disorders can have a significant clinical impact. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

Carrier Screening [Panel] Recommendations

American College of Obstetricians and Gynecologists

The ACOG (2017; reaffirmed in 2023) made the following recommendations on expanded (i.e., non-targeted) carrier screening:(17)

“Ethnic-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy 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 (i.e., they will miss carrier state in up to 10% of low-risk populations) or hemoglobinopathies.

In 2015, a joint statement on extended carrier screening was issued by the 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 health care 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 three common Ashkenazi mutations. Currently, hexosaminidase An 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 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
- Offer 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 a family or personal medical history warrants.
- The consent process should include elements of pre- and post-test counseling
- Ninety-seven genes in autosomal recessive conditions and sixteen genes in x-linked conditions were identified as being appropriate for carrier screening (see Tables 8-10)
- All patients should be offered screening for only those x-linked genes listed in Table 10 as part of Tier 3 screening.
- Ongoing curation of Tier 3 x-linked genes with input from:
    - ACMG Committees and Work Groups;
    - Additional professional organizations and the lay public as appropriate.
- Providers are comfortable discussing the following in pretest counseling:
    - Carrier screening is optional and can be performed at any time.
    - Preconception screening is recommended over prenatal screening.
    - When reproductive partner has changed, carrier screening should be readdressed.
    - Carrier screening is not a test for all genetic conditions.
    - Genetic variants have likely been in a family for many generations.
    - Carrier screening will NOT identify de novo variants in offspring.
    - Carrier screening does NOT replace newborn screening.
    - When Tier 1 or Tier 2 carrier screening was performed in a prior pregnancy, Tier 3 screening should be offered.
    - A carrier of an autosomal recessive condition will rarely manifest any clinical signs or symptoms of that condition.
    - Consanguineous couples have an increased risk to be carriers for the same condition.
    - All genes and variants that cause a condition may not be known and may not be examined as part of Tier 3 or Tier 4 screening. If family history warrants, additional genes may be considered for evaluation and referral to a genetics professional should be considered. A negative test reduces the chance to have an affected child but does not eliminate the risk.
    - In some situations, X-linked heterozygous patients will manifest signs and symptoms that are different than the condition seen in offspring

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

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)

Refer to Table 8 for additional details regarding appropriate autosomal recessive conditions for screening and their associated carrier frequencies.

Table 8. ACMG - Frequency of Autosomal Recessive Genes and Recommended Screenings

Autosomal recessive genes for screening with carrier frequency				
OMIM gene	***OMIM gene name***	***Maximum carrier frequency***	***OMIM phenotype***	***Conditions***
Genes for Screening with Carrier Frequency of ≥ 1/50				
141900	*HBB*	0.119837	603903	Sickle cell anemia β-thalassemia
			613985	
613208	*XPC*	0.050885	278720	Xeroderma pigmentosum
606933	*TYR*	0.049337	203100	Oculocutaneous albinism type 1A and 1B
			606952	
613815	*CYP21A2*	0.048459	201910	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency
612349	*PAH*	0.046068	261600	Phenylketonuria
602421	*CFTR*	0.040972	219700	Cystic fibrosis
600985	*TNXB*	0.035134	606408	Ehlers–Danlos-like syndrome due to tenascin-X deficiency
606869	*HEXA*	0.033146	272800	Tay–Sachs disease
121011	*GJB2*	0.026200	220290	Non-syndromic hearing loss recessive 1A
			601544	Non-syndromic hearing loss dominant 3A
602858	*DHCR7*	0.023709	270400	Smith–Lemli–Opitz syndrome
277900	*ATP7B*	0.021983	606882	Wilson disease
608034	*ASPA*	0.019856	271900	Canavan disease
607008	*ACADM*	0.016583	201450	Medium-chain acyl-coenzyme A dehydrogenase deficiency
602716	*NPHS1*	0.015994	256300	Finnish congenital nephrotic syndrome
601785	*PMM2*	0.015877	212065	Carbohydrate-deficient glycoprotein syndrome type Ia
607440	*FKTN*	0.015660	611615	Cardiomyopathy, dilated, 1X
			253800	Walker–Warburg congenital muscular dystrophy
605646	*SLC26A4*	0.015422	600791	Deafness autosomal recessive 4
			274600	Pendred syndrome
126340	*ERCC2*	0.015255	610756	Cerebrooculofacioskeletal syndrome 2
			601675	Trichothiodystrophy 1, photosensitive
603297	*DYNC2H1*	0.014817	613091	Short-rib thoracic dysplasia 3 with or without polydactyly
Genes for Screening with Carrier Frequency of <1/50 to ≥1/100				

610142	*CEP290*	0.014422	610188	Joubert syndrome 5
			611755	Leber congenital amaurosis 10
607839	*GBE1*	0.013799	232500	Glycogen storage disease, type IV
			263570	GBE1-related disorders
606800	*GAA*	0.013565	232300	Glycogen storage disease, type II (Pompe disease)
100725	*CHRNE*	0.013526	100725	Myasthenic syndrome, congenital, 4A, slow-channel
				Myasthenic syndrome, congenital, 4B, fast-channel
613742	*G6PC*	0.013401	232200	Glycogen storage disease type IA
611409	*OCA2*	0.013113	203200	Oculocutaneous albinism brown and type II
120120	*COL7A1*	0.012995	226600	Recessive dystrophic epidermolysis bullosa
600509	*ABCC8*	0.012242	618857	Diabetes mellitus, permanent neonatal 3
612724	*ALDOB*	0.012119	229600	Hereditary fructosuria
613899	*FANCC*	0.011992	227645	Fanconi anemia, complementation group C
604597	*GRIP1*	0.011989	617667	Fraser syndrome
248611	*BCKDHB*	0.011760	245600	Maple syrup urine disease
613726	*ANO10*	0.010781	613728	Spinocerebellar ataxia 10
104170	*NAGA*	0.010637	609241	Schindler disease, type 1
				Schindler disease, type 3
607608	*SMPD1*	0.010259	257200	Niemann–Pick disease, type A
			607616	Niemann–Pick disease, type B
608400	*USH2A*	0.010203	276901	Usher syndrome, type 2A
609058	*MMUT*	0.009999	251000	Methylmalonic aciduria–methylmalonyl–CoA mutase deficiency
600650	*CPT2*	0.009742	600649	Carnitine palmitoyltransferase II deficiency, infantile
			608836	Carnitine palmitoyltransferase II deficiency, lethal neonatal
608894	*AHI1*	0.009740	608629	Joubert syndrome 3
Genes for Screening with Carrier Frequency of <1/100 to ≥1/150				
608172	*DHDDS*	0.009340	613861	Congenital disorder of glycosylation type 1
				Retinitis pigmentosa 59
606152	*SLC19A3*	0.009163	607483	Basal ganglia disease, biotin-responsive
606999	*GALT*	0.009132	230400	Galactosemia
118485	*CYP11A1*	0.008771	613743	Adrenal insufficiency, congenital, with 46, XY sex reversal, partial or complete
190000	*TF*	0.008615	209300	Atransferrinemia
609831	*MMACHC*	0.008610	277400	Methylmalonic aciduria with homocystinuria cblC type
601615	*ABCA3*	0.008587	610921	Surfactant metabolism dysfunction, pulmonary 3
606463	*GBA*	0.008572	230800	Gaucher disease, type I
			230900	Gaucher disease, type II
605248	*MCOLN1*	0.008531	252650	Mucolipidosis type IV
607840	*GNPTAB*	0.008454	252500	Mucolipidosis type II alpha/beta
			252600	Mucolipidosis type III alpha/beta
613228	*AGA*	0.008364	208400	Aspartylglucosaminuria
605514	*PCDH15*	0.008330	609533	Deafness, autosomal recessive 23
			602083	Usher syndrome, type 1F
613871	*FAH*	0.007716	276700	Tyrosinemia type I

607358	*AIRE*	0.007664	240300	Autoimmune polyendocrinopathy syndrome type I
606151	*BBS2*	0.007501	615981	Bardet–Biedl syndrome 2
			616562	Retinitis pigmentosa 74
606530	*CYP27A1*	0.007399	213700	Cerebrotendinous xanthomatosis
611204	*CCDC88C*	0.007282	236600	Congenital hydrocephalus 1
136132	*FMO3*	0.007190	602079	Trimethylaminuria
613277	*TMEM216*	0.007107	608091	Joubert syndrome 2
			603194	Meckel syndrome 2
605080	*CNGB3*	0.006849	262300	Achromatopsia 3
607117	*MCPH1*	0.006822	651200	Primary microcephaly 1, recessive
602671	*SLC37A4*	0.006748	232220	Glycogen storage disease Ib
			232240	Glycogen storage disease Ic
170280	*PRF1*	0.006734	603553	Hemophagocytic lymphohistiocytosis, familial, 2
604272	*SCO2*	0.006671	604377	Mitochondrial complex IV deficiency, nuclear type 2
604285	*AGXT*	0.006648	259900	Hyperoxaluria, primary type I
Genes for Screening with Carrier Frequency of <1/150 to ≥1/200				
609575	*ACADVL*	0.006419	201475	Very long chain acyl-CoA dehydrogenase deficiency
608310	*ASL*	0.006190	207900	Argininosuccinate aciduria
607261	*EVC2*	0.006083	225500	Chondroectodermal dysplasia
607574	*ARSA*	0.005986	250100	Metachromatic leukodystrophy
251170	*MVK*	0.005966	260920	Hyper-IgD syndrome
			610377	Mevalonic aciduria
606702	*PKHD1*	0.005960	263200	Autosomal recessive polycystic kidney disease
609019	*BTD*	0.005953	253260	Biotinidase deficiency
171760	*ALPL*	0.005719	146300	Hypophosphatasia, adult
			241510	Hypophosphatasia, childhood and infantile
209901	*BBS1*	0.005713	209900	Bardet–Biedl syndrome 1
118425	*CLCN1*	0.005688	255700	Congenital myotonia, autosomal recessive form
609506	*CYP27B1*	0.005512	264700	Vitamin D–dependent rickets, type 1
174763	*POLG*	0.005330	203700	Mitochondrial DNA depletion syndrome 4A
			613662	Mitochondrial DNA depletion syndrome 4B
609014	*MCCC2*	0.005184	210210	3-methylcrotonyl CoA carboxylase 2 deficiency
605908	*MLC1*	0.005058	604004	Megalencephalic leukoencephalopathy with subcortical cysts
607809	*ACAT1*	0.005000	203750	α-Methylacetoacetic aciduria
612013	*CC2D2A*	0.004969	612285	Joubert syndrome 9
			612284	Meckel syndrome 6
606718	*SLC26A2*	0.004715	226900	Epiphyseal dysplasia, multiple, 4
			600972	Achondrogenesis Ib
236200	*CBS*	0.004676	236200	Homocystinuria, B6 responsive and nonresponsive
600073	*LRP2*	0.004676	222448	Donnai–Barrow syndrome
252800	*IDUA*	0.004675	607014	Mucopolysaccharidosis, Ih (Hurler S)
			607015	Mucopolysaccharidosis, Ih/s (Hurler–Scheie S)
606596	*FKRP*	0.004668	613153	Muscular dystrophy–dystroglycanopathy, type

				A, 5
			606612	Muscular dystrophy–dystroglycanopathy, type B, 5
610326	*RNASEH2B*	0.004609	610181	Aicardi Goutieres syndrome 2
611524	*RARS2*	0.004592	611523	Pontocerebellar hypoplasia type 6

OMIM Online Mendelian Inheritance in Man.

Table 9. Genes that were ascertained for screening outside of the gnomAD criteria[a]

OMIM gene	*OMIM gene name*	Published carrier frequency[b]	Rationale for inclusions	Ethnic group	OMIM phenotype	Conditions
141800	*HBA1*	U[c]	Carrier frequency	SEA and others	604131	α-Thalassemia
141850	*HBA2*	U[c]	Carrier frequency	SEA and others	604131	α-Thalassemia
600354	*SMN1*	1/60	ACOG, ACMG and carrier frequency	US panethnic	253300	
					253550	Spinal muscular
					253400	atrophy types: I, II, III, IV
					271150	
604982	*HPS1*	1/59	Carrier frequency	PR	203300	Hermansky Pudlak S. 1
606118	*HPS3*	1/59	Carrier frequency	PR	614072	Hermansky Pudlak S. 3
603722	*ELP1* "Formerly known as *IKBKAP"*	1/32	ACOG, ACMG and carrier frequency	AJ	223900	Familial dysautonomia
606829	*FXN*	1/60–1/100	Carrier frequency	Caucasians[d]	229300	Friedreich ataxia
238331	*DLD*	~1/100	Carrier frequency	AJ	246900	Dihydrolipoamide dehydrogenase deficiency
161650	*NEB*	1/168	Carrier frequency	AJ	256030	Nemaline myopathy 2
606397	*CLRN1*	1/120	Carrier frequency	AJ	276902	Usher syndrome 3a
604610	*BLM*	1/100	ACMG and carrier frequency	AJ	210900	Bloom syndrome

ACMG American College of Medical Genetics and Genomics, ACOG American College of Obstetricians and Gynecologists, AJ Ashkenazi Jewish (≥2% of the US population), OMIM Online Mendelian Inheritance in Man[31] PR Puerto Rican, SEA South East Asian.

[a]Carrier frequency of a sequence variant is <1/200, if reported in gnomAD.[20]

[b]Diagnostic laboratory data was not used for carrier frequency data.

[c]Specific data for general US population not available; however, recognized as common among many US immigrant populations.[32]

[d]This term is no longer used by the journal but is used in the original article to which these studies refer. We have therefore not changed the term but recognize it does not accurately describe the ancestry of the populations originally studied.[33]

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. See Table 10 for further details

Table 10. Appropriate Tier 3 X-Linked Genes and the Associated Phenotype

OMIM gene	OMIM gene name	OMIM phenotype	Phenotype
300371	*ABCD1*	300100	Adrenoleukodystrophy (ALD)
300806	*AFF2*	309548	Mental retardation, X-linked, associated with fragile site FRAXE
300382	*ARX*	308350	Developmental and epileptic encephalopathy 1 (DEE1)
300377	*DMD*	300376	Muscular dystrophy, Becker type (BMD)
		310200	Muscular dystrophy, Duchenne type (DMD)
306700	*F8*	300841	Hemophilia A (HEMA)
300746	*F9*	306900	Hemophilia B (HEMB)
309550	*FMR1*	300624	Fragile X syndrome (FXS)
300644	*GLA*	301500	Fabry disease
308840	*L1CAM*	307000	Hydrocephalus due to congenital stenosis of aqueduct of Sylvius (HSAS)
300552	*MID1*	300000	Opitz GBBB syndrome, type I (GBBB1)
300473	*NR0B1*	300200	Adrenal hypoplasia, congenital (AHC)
300461	*OTC*	311250	Ornithine transcarbamylase deficiency
300401	*PLP1*	312920	Spastic paraplegia 2, X-linked (SPG2)
312610	*RPGR*	300029	Retinitis pigmentosa 3 (RP3; RP)
		300455	Retinitis pigmentosa, X-linked, and sinorespiratory
		300834	Infections, with or without deafness
			Macular degeneration, X-linked atrophic
300839	*RS1*	312700	Retinoschisis 1, X-linked, juvenile (RS1)
300036	*SLC6A8*	300352	Cerebral creatine deficiency syndrome 1 (CCDS1)

OMIM Online Mendelian Inheritance in Man[31]

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

- The content of carrier screening panels and the 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.

Carrier screening was recommended for individuals of Ashkenazi Jewish descent (10) for the following conditions:

- Cystic fibrosis
- Canavan disease
- Familial dysautonomia
- Tay-Sachs disease
- Fanconi anemia (group C)
- Niemann-Pick (type A)
- Bloom syndrome
- Mucolipidosis IV
- Gaucher disease

According to ACMG,(10) 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.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 11.

Table 11. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04157595	Mackenzie's Mission: The Australian Reproductive Carrier Screening Project	20,000	Dec 2023 (ongoing)
Unpublished			
NCT01902901	Clinical Implementation of Carrier Status Using Next Generation Sequencing	384	May 2018

NCT: national clinical trial

Government Regulations

National:

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

Local:

There is no local coverage determination on this topic

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(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Gene Expression Profiling for Cutaneous Melanoma
- Genetic and Protein Biomarkers for the Diagnosis And Cancer Risk Assessment of Prostate Cancer
- Genetic Cancer Susceptibility Panel Using Next Generation Sequencing
- Genetic, Miscellaneous and Genetic and Molecular Diagnostic Tests
- Genetic Testing – Preimplantation
- Genetic Testing – Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
- Genetic Testing and Counseling
- Genetic Testing for Alpha-1 Antitrypsin Deficiency

- Genetic Testing for Alzheimer's Disease
- Genetic Testing for Amyotrophic Lateral Sclerosis
- Genetic Testing for Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)
- Genetic Testing for Bloom Syndrome
- Genetic Testing for Cardiac Ion Channelopathies
- Genetic Testing for Cystic Fibrosis
- Genetic Testing for FMR1 Mutations (Including Fragile X Syndrome)
- Genetic Testing for CHEK2 Mutations for Breast Cancer
- Genetic Testing for Dilated Cardiomyopathy
- Genetic Testing for Ducheene and Becker Muscular Dystrophy
- Genetic Testing for Epilepsy
- Genetic Testing for Familial Cutaneous Malignant Melanoma (CDKN2A)
- Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and other High-Risk Cancers
- Genetic Testing for Hereditary Hearing Loss
- Genetic Testing for Hereditary Hemochromatosis
- Genetic Testing for Heterozygous Familial Hypercholesterolemia
- Genetic Testing for Inherited Hypertrophic Cardiomyopathy
- Genetic Testing for Inherited Thrombophilias
- Genetic Testing for Lynch Syndrome
- Genetic Testing for Marfan, Thoracic Aortic Aneurysms and Dissections, and Related Disorders
- Genetic Testing for Mitochondrial Disorders
- Genetic Testing for Myotonic Muscular Dystrophy
- Genetic Testing for Noonan Spectrum Disorder
- Genetic Testing for Prader-Willi and Angelman Syndromes (Chromosome 15 Abnormalities)
- Genetic Testing for PTEN Hamartoma Tumor Syndrome
- Genetic Testing for Retinal Dystrophies
- Genetic Testing for Rett Syndrome
- Genetic Testing for Tay Sachs Disease
- Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

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Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/15	8/18/15	9/14/15	Joint policy established
11/1/16	8/16/16	8/16/16	• Routine maintenance • Inclusion criteria clarified
11/1/17	8/15/17	8/15/17	• Routine maintenance • Policy extensively revised from a "concept review" to an evidence review incorporating a literature review through March 9, 2017, and 2017 ACOG Committee Opinions. Multiple references added. • Added "All targeted screening not meeting any of the above criteria" to the exclusions. • Changed title from Genetic Testing for Carrier Status to Genetic Testing - Carrier Screening for Genetic Diseases. • Updated local Medicare information.
11/1/18	8/21/18	8/21/18	• Routine maintenance
11/1/19	8/20/19		• Routine maintenance
11/1/20	8/18/20		• Routine maintenance
11/1/21	10/20/21		• Routine maintenance • Panethnic panel language adopted • Diverge from BCBSA in favor of ACMG – "at risk" and "ethnically based" screening criteria removed from panethnic testing • 81412 and 81443 added to policy • Partner risk clarified • Policy guideline section created
5/1/22	3/11/22		• Criteria clarified • Replaced policy for Alpha Thalassemia

5/1/23	2/21/23		• Routine maintenance (slp) • Vendor Managed: N/A
5/1/24	2/20/24		• Routine maintenance (slp) • Vendor managed: N/A • 0400U added as EI • Clarified that ELP1 is formerly known as IKBKAP.
1/1/25	10/15/24		• 0449U added as EI (transferred from GT- Noninvasive Prenatal Screening)

Next Review Date: 1st Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING - CARRIER SCREENING FOR GENETIC DISEASES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to Medicare information under Government Regulations
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.