Clinical Policy: Genetic Testing Prenatal and Preconception Carrier Screening

Reference Number: LA.CP.MP.234 **Coding Implications**
Date of Last Revision: 02/22 **Revision Log**

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

There are more than 1,300 inherited recessive disorders (autosomal or X-linked) that affect 30 out of every 10,000 children. Some diseases have limited impact on either length or quality of life, while others are uniformly fatal in infancy or childhood. By definition, autosomal recessive disorders arise when both parents pass on disease-causing copies of genes to a child. X-linked recessive conditions arise when a disease-causing version of a gene is on the X-chromosome and is passed to a male child who only has one copy of the X-chromosome.

Carrier screening is performed to identify individuals at risk of having offspring with inherited recessive or X-linked single-gene disorders. Carriers are typically asymptomatic but can pass disease-causing variants to their offspring. Carrier screening may be performed in the prenatal or preconception periods. Risk-based carrier screening is performed in individuals who have an increased risk to be a carrier based on population carrier frequency, ethnicity, and/or family history.

Expanded carrier screening (ECS) involves screening individuals or couples for disorders in many genes simultaneously (up to 100s) by next-generation sequencing. ECS panels may screen for diseases that are present with increased frequency in specific populations, but also include a wide range of diseases for which the individual seeking testing is not at increased risk for positive carrier status. The conditions included on ECS panels are not standardized and the panels may include conditions that are not well understood and for which there are no existing professional guidelines.

Below are a list of higher volume tests and the associated laboratories for each criteria section. This list is not all inclusive.

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81443	Foresight (Myriad) Horizon (Natera) Inheritest (LabCorp) GeneSeq (LabCorp) Comprehensive Carrier Screening (Invitae)	Expanded Carrier Screening Panels	O09, Z13, Z31, Z34, Z36, Z84

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81221,81220	*CFTR* Known Familial Mutation Analysis	CFTR Known Familial Variant Analysis	O09, Z13, Z31, Z34, Z36, Z84
81222, 1223, S3835	*CFTR* Sequencing Tests *CFTR* Deletion/Duplication Tests *CFTR* Common Mutation Tests	CFTR Sequencing and/or Deletion/Duplication Analysis, or Mutation Panel	O09, Z13, Z31, Z34, Z36, Z84
81224	*CFTR* Intron 9 (8) Poly-T Analysis	CFTR Intron 9 PolyT and TG Analysis (aka Intron 8 poly-T/TG)	O09, Z13, Z31, Z34, Z36, Z84
81337,81400, 81403	*SMN1* Targeted Mutation Analysis Tests	SMN1 Targeted Variant Analysis	O09, Z13, Z31, Z34, Z36, Z84
81329,81336, 81405	*SMN1* Deletion/Duplication (SMA Carrier Screening) Tests	SMN1 Sequencing and/or Deletion/Duplication Analysis	O09, Z13, Z31, Z34, Z36, Z84
81243, 81244	*FMR1* Repeat Analysis Tests *FMR1* Carrier Screening Tests *FMR1* Repeat and Methylation Analysis Tests	FMR1 Repeat Analysis	O09, Z13, Z31, Z34, Z36, Z84
81258,81362, 81257, 81361	*HBA1* Targeted Mutation Analysis Tests *HBA2* Targeted Mutation Analysis Tests *HBB* Targeted Mutation Analysis Tests	HBA1, HBA2, or HBB Targeted Variant Analysis	Z31
81259,81269, 81363, 81364	*HBA1* Sequencing Tests *HBA2* Sequencing Tests *HBB* Sequencing Tests	HBA1, HBA2, or HBB Targeted Variant Analysis	Z31

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
	HBA1 **Deletion/Duplication Tests** ***HBA1*** **Deletion/Duplication Tests** ***HBB*** **Deletion/Duplication Tests**		
81412, 81443	Foresight: AJ Panel (Counsyl) Inheritest: AJ Panel (LabCorp) Horizon 106 Comprehensive Jewish Panel (Natera)	Ashkenazi Jewish Carrier Panel Testing	O09, Z13, Z31, Z34, Z36, Z84
81403	***DMD*** **Targeted Mutation Analysis Tests**	DMD Targeted Variant Analysis	Z31
81161, 81408, 0218U	***DMD*** **Deletion/Duplication Tests** ***DMD*** **Sequencing Tests**	DMD Sequencing and/or Deletion/Duplication Analysis	Z31
81174,81190, 81200, 81205, 81209, 81242, 81247, 81248, 81250, 81251, 81253, 81254, 81289, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408	Varies	General Criteria for Targeted Carrier Screening	Z14, Z15, Z31

~~This policy document provides criteria for Prenatal and Preconception Carrier Screening. Please refer to:~~

- ~~*CP.MP.235 Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss* for coverage related to prenatal and pregnancy loss diagnostic genetic testing intended to diagnose genetic conditions following amniocentesis, chorionic villus sampling, or pregnancy loss.~~
- ~~*CP.MP.231 Genetic Testing: Noninvasive Prenatal Screening (NIPS)* for coverage criteria related to prenatal cell-free DNA screening tests.~~

- ~~*CP.MP.233 Genetic Testing: Preimplantation Genetic Testing* for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.~~
- ~~*CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability and Developmental Delay* for coverage criteria related to suspected multisystem genetic conditions in the postnatal period.~~
- ~~*CP.MP.223 Genetic Testing: Hearing Loss* for coverage related to diagnostic genetic testing for hereditary hearing loss.~~
- ~~*CP.MP.224 Genetic Testing: Hematologic Conditions (non-cancerous)* for coverage related to diagnostic genetic testing for alpha-thalassemia and other hemoglobinopathies.~~
- ~~*CP.MP.229 Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders* for coverage related to diagnostic genetic testing for mitochondrial and other disorders.~~
- ~~*CP.MP.222 Genetic Testing: General Approach to Genetic Testing* for coverage criteria related to carrier screening that is not specifically discussed in this or other non-general policies.~~

Policy/Criteria

Expanded Carrier Screening Panels

I. It is the policy of health plans affiliated with Louisiana Healthcare Connections that expanded carrier screening panels (81443) may be considered medically necessary when meeting all of the following:

A. At least one of the following:

1. The member/enrollee is considering pregnancy or is currently pregnant,

2. The member/enrollee's reproductive partner is a known carrier for two or more recessive conditions,

B. The panel includes 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*),

C. The panel includes *CFTR and SMN1*,

D. The panel does not include genes associated with known adult-onset conditions, including but not limited to, hereditary cancer syndromes (e.g., Hereditary Breast and Ovarian Cancer Syndrome, Lynch Syndrome), dementia (e.g., Alzheimer's Disease, Huntington's Disease), blood clotting disorders (e.g., Factor V Leiden),

E. **The panel has been ordered by and the member/enrollee has received genetic counseling from one of the following (who is not affiliated with the commercial testing laboratory, if applicable):**

1. **A board-certified medical geneticist**
2. **Maternal-fetal medicine specialist/perinatologist**
3. **A board-certified OBGYN**
4. **A board-certified genetic counselor**
5. **An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology**

II. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support expanded carrier screening panels (81443) for all other indications.**

Cystic Fibrosis Carrier Screening

***CFTR* Known Familial Variant Analysis**

I. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that cystic fibrosis carrier screening via *CFTR* targeted mutation analysis for a known familial mutation (81221) may be considered medically necessary when meeting both of the following:**

A. **The member/enrollee and/or the member/enrollee's reproductive partner is considering pregnancy or is currently pregnant,**

B. **The member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant in *CFTR*.**

II. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support cystic fibrosis carrier screening via *CFTR* targeted mutation analysis for a known familial mutation (81221) for all other indications.**

***CFTR* Sequencing, Deletion/Duplication Analysis, or Mutation Panel**

I. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that cystic fibrosis carrier screening via *CFTR* sequencing (81223, S3835), deletion/duplication analysis (81222), or a mutation panel (81220) using at a minimum the ACMG-23 variant panel, may be considered medically necessary when meeting either of the following:**

A. **The member/enrollee and/or the member/enrollee's reproductive partner is considering pregnancy or is currently pregnant,**

B. **The member/enrollee's reproductive partner is a known carrier for cystic fibrosis.**

II. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support cystic fibrosis carrier screening via *CFTR***

sequencing (81233, S3835), deletion/duplication analysis (81222), or a mutation panel (81220) using at a minimum the ACMG-23 variant panel, for all other indications.

***CFTR* Intron 9 PolyT and TG Analysis (previously called Intron 8 polyT/TG Analysis)**

I. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that analysis of the *CFTR* intron 9 polyT and TG regions (81224) for cystic fibrosis carrier screening may be considered medically necessary when meeting both of the following:**

   A. **The member/enrollee and/or the member/enrollee's reproductive partner is considering pregnancy or is currently pregnant,**

   B. **The member/enrollee is known to have an R117H variant in the CFTR gene.**

II. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support analysis of the *CFTR* intron 9 polyT and TG regions (81224) for cystic fibrosis carrier screening for all other indications.**

~~**Note: Refer to *CP.MP.230 Genetic Testing for Multisystem Inherited Disorders, Intellectual Disability and Developmental Delay* for criteria for genetic testing to establish a diagnosis of cystic fibrosis.**~~

Spinal Muscular Atrophy Carrier Screening
***SMN1* Targeted Variant Analysis**

I. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that spinal muscular atrophy (SMA) carrier screening via *SMN1* targeted variant analysis (81337, 81400, 81403) may be considered medically necessary when meeting both of the following:**

   A. **The member/enrollee and/or the member/enrollee's reproductive partner is considering pregnancy or is currently pregnant,**

   B. **The member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant in *SMN1*.**

II. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support spinal muscular atrophy (SMA) carrier screening via *SMN1* targeted variant analysis (81337, 81400, 81403) for all other indications.**

***SMN1* Sequencing and/or Deletion/Duplication Analysis**

I. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that spinal muscular atrophy (SMA) carrier screening via *SMN1* sequencing and/or deletion/duplication analysis (81329, 81336, 81405) is considered medically necessary when meeting either of the following:**

   A. **The member/enrollee and/or member/enrollee's reproductive partner is considering pregnancy or is currently pregnant,**

B. The member/enrollee's reproductive partner is a known carrier for spinal muscular atrophy.

II. It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support spinal muscular atrophy (SMA) carrier screening via *SMN1* sequencing and/or deletion/duplication analysis (81329, 81336, 81405) for all other indications.

~~Note: Refer to *CP.MP.218 Genetic Testing for Epilepsy, Neuromuscular, and Neurodegenerative Disorders* for criteria for genetic testing to establish a diagnosis of spinal muscular atrophy (SMA).~~

Fragile X Syndrome Carrier Screening
***FMR1* Repeat Analysis**

I. It is the policy of health plans affiliated with Louisiana Healthcare Connections that Fragile X carrier screening via *FMR1* CGG-trinucleotide repeat analysis (81243, 81244) may be considered medically necessary when meeting either of the following:

A. The member/enrollee has been diagnosed with premature ovarian insufficiency or elevated follicle-stimulating hormone level before age 40 years,

B. The member/enrollee is considering a pregnancy or is currently pregnant and has one of the following:

1. Close relative[1] with Fragile X syndrome (i.e., close relative has >200 CGG repeats in the *FMR1* gene),
2. Close relative[1] who is a known carrier for Fragile X syndrome (i.e., close relative has between 55-200 CGG repeats in the *FMR1* gene),
3. Close relative[1] with unexplained intellectual disability, developmental delay, or autism spectrum disorder,
4. Close relative[1] diagnosed with premature ovarian insufficiency or elevated follicle-stimulating hormone level before age 40 years.

II. It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support Fragile X carrier screening via *FMR1* CGG-trinucleotide repeat analysis (81243, 81244) for all other indications.

~~Note: Refer to *CP.MP.230 Genetic Testing for Multisystem Inherited Disorders, Intellectual Disability and Developmental Delay* for criteria for genetic testing to establish a diagnosis of fragile X syndrome.~~

Hemoglobinopathy Carrier Screening
***HBA1*, *HBA2*, or *HBB* Targeted Variant Analysis**

I. It is the policy of health plans affiliated with Louisiana Healthcare Connections that hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81257, 81258, S3845, S3846),

or *HBB* (81361, 81362) targeted variant analysis may be considered medically necessary when meeting both of the following:

A. The member/enrollee and/or the member/enrollee's reproductive partner is considering pregnancy or is currently pregnant,

B. The member/enrollee meets one of the following:

1. The member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant in *HBA1*, *HBA2*, or *HBB*,

2. The member/enrollee's reproductive partner is a known carrier of a pathogenic or likely pathogenic variant in *HBA1*, *HBA2*, or *HBB*,

3. The member/enrollee's reproductive partner is known to have a diagnosis of a hemoglobinopathy,

4. The member/enrollee's hematologic screening results (e.g., MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) are suggestive of or do not conclusively rule out a hemoglobinopathy.

II. It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81257, 81258, S3845, S3846), or *HBB* (81361, 81362) targeted variant analysis for all other indications.

***HBA1*, *HBA2*, or *HBB* Sequencing and/or Deletion/Duplication Analysis**

I. It is the policy of health plans affiliated with Louisiana Healthcare Connections that hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81259, 81269, S3845), or *HBB* (81363, 81364, S3846) sequencing and/or deletion/duplication analysis may be considered medically necessary when meeting both of the following:

A. The member/enrollee and/or the member/enrollee's reproductive partner is considering pregnancy or is currently pregnant,

B. The member/enrollee meets one of the following:

1. The member/enrollee's hematologic screening results (e.g., MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) are suggestive of or do not conclusively rule out a hemoglobinopathy.

II. It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81259, 81269, S3845), or *HBB* (81363, 81364, S3846) sequencing and/or duplication analysis for all other indications.

~~**Note: Refer to *CP.MP.224 Genetic Testing for Hematologic Disorders (non-cancerous)* for criteria for genetic testing to establish a diagnosis of a hemoglobinopathy.**~~

Ashkenazi Jewish Carrier Panel Testing

I. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that Ashkenazi Jewish carrier panel testing (81412) may be considered medically necessary when meeting all of the following:**

   A. **The member/enrollee and/or the member/enrollee's reproductive partner is considering pregnancy or is currently pregnant,**

   B. **The member/enrollee is of Ashkenazi Jewish ancestry,**

   C. **The panel includes, at a minimum, screening for carrier status for genetic conditions associated with the following genes, as recommended by the American College of Medical Genetics (ACMG):**

      1. **Tay Sachs disease (HEXA)**
      2. **Canavan disease (ASPA)**
      3. **Cystic fibrosis (CFTR)**
      4. **Familial dysautonomia (ELP1)**
      5. **Bloom syndrome (BLM)**
      6. **Fanconi anemia (FANCC)**
      7. **Niemann-Pick disease (SMPD1)**
      8. **Gaucher disease (GBA)**
      9. **Mucolipidosis IV (MCOLN1)**

Note: If only one partner is of Ashkenazi Jewish ancestry, then testing of that partner is considered medically necessary. Testing of the other partner is considered medically necessary only if the result of testing of the Ashkenazi Jewish partner is positive.

Duchenne And Becker Muscular Dystrophy Carrier Screening
***DMD* Targeted Variant Analysis**

I. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that Duchenne and Becker muscular dystrophy carrier screening via *DMD* targeted variant analysis (81403) may be considered medically necessary when meeting both of the following:**

   A. **The member/enrollee is considering pregnancy or is currently pregnant,**

   B. **The member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant in *DMD*.**

II. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support Duchenne and Becker muscular dystrophy carrier screening via *DMD* targeted variant analysis (81403) for all other indications.**

DMD Sequencing and/or Deletion/Duplication Analysis

I. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that Duchenne and Becker muscular dystrophy carrier screening via _DMD_ sequencing and/or deletion/duplication analysis (81161, 81408) may be considered medically necessary when meeting both of the following:**

   A. **The member/enrollee is considering pregnancy or is currently pregnant,**

   B. **The member/enrollee has one of the following:**

      1. **First[1a]- or second-degree[1b] male relative diagnosed with Duchenne or Becker muscular dystrophy.**

II. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support Duchenne and Becker muscular dystrophy carrier screening via _DMD_ sequencing and/or deletion/duplication analysis (81161, 81408) for all other indications.**

~~**Note: Refer to _CP.MP.218 Genetic Testing for Epilepsy, Neuromuscular, and Neurodegenerative Disorders_ for criteria for genetic testing to establish a diagnosis of Duchenne or Becker muscular dystrophy.**~~

General Criteria For Carrier Screening

NOTE: Each section in the policy reference table includes specific criteria. For any prenatal or preconception carrier screening test that does not have specific criteria above, refer to the following criteria to assess for medical necessity.

Targeted carrier screening is defined as a test that screens for a known mutation in one gene associated with a specific genetic condition.

I. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that carrier screening for a genetic disorder (81174, 81190, 81200, 81205, 81209, 81242, 81247, 81248, 81250, 81251, 81253, 81254, 81289, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408) may be considered medically necessary when meeting all of the following:**

   A. **The member/enrollee is considering pregnancy or is currently pregnant,**

   B. **The genetic disorder is a recessive condition,**

   C. **One of the following:**

      1. **The member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant associated with the disorder,**

      2. **The member/enrollee's reproductive partner is a carrier for the genetic disorder,**

3. **The member/enrollee or the member/enrollee's reproductive partner are member/enrollees of a population known to have a carrier rate of 1% or higher for the genetic condition,**

4. **The member/enrollee or the member/enrollee's reproductive partner has a first[1a]- or second-degree[1b] relative who is affected with the genetic disorder.**

II. **It is the policy of health plans affiliated with Louisiana Healthcare Connections that current evidence does not support carrier screening for a genetic disorder (81174, 81190, 81200, 81205, 81209, 81242, 81247, 81248, 81250, 81251, 81253, 81254, 81289, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408) when the member/enrollee does not meet any criteria above.**

Notes and Definitions

1. **Close relatives include first, second, and third degree blood relatives:**

   a. **First-degree relatives are parents, siblings, and children**

   b. **Second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings**

   c. **Third-degree relatives are great grandparents, great aunts, great uncles, great grandchildren, and first cousins**

"Negative" carrier screening results reduce, but do not eliminate, the chance of an individual being a carrier for the condition(s) screened. Therefore, there is still a "residual risk" of being a carrier for the condition(s) screened. The residual risk is the chance that the individual is still a carrier based on a normal/negative carrier screen. The residual risk will vary depending on which test is performed, how many mutations are included for each condition, the patient's ethnicity, etc.

It is important to recognize that family history, ethnicity, and race are self-reported, and may not be completely accurate, particularly in multi-ethnic and multi-racial societies.

When one member of a couple is at high risk of being a carrier for a certain condition due to ancestry (e.g., Ashkenazi Jewish, French-Candian, Cajun, etc.) or has a family history of a condition, the high-risk partner should be offered screening. If the high-risk partner is found to be a carrier, the other partner should then be offered screening.

Genetic counseling is strongly recommended for patients considering expanded carrier screening.

Background

American College of Medical Genetics and Genomics (ACMG):

Expanded Carrier Screening Panels

ACMG published a practice resource (2021) regarding screening for autosomal recessive and X-linked conditions during pregnancy and preconception, which included the following recommendations:

- **The phrase "expanded carrier screening" be replaced by "carrier screening".**
- **Adopting a more precise tiered system based on carrier frequency**
  - **Tier 1: CF + SMA + Risk Based Screening**
  - **Tier 2: ≥1/100 carrier frequency (includes Tier 1)**
  - **Tier 3: ≥ 1/200 carrier frequency (includes Tier 2) includes X-linked conditions**
  - **Tier 4: <1/200 carrier frequency (includes Tier 3) genes/condition will vary by lab**
- **All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening.**
- **Tier 4 screening should be considered:**
  - **When a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer)**
  - **When a family or personal medical history warrants.**

ACMG does not recommend:

- **Offering only 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.**

ACMG published a position statement on prenatal/preconception expanded carrier screening in 2013, which stated:

"The proper selection of appropriate disease-causing targets for general population-based carrier screening (i.e., absence of a family history of the disorder) should be developed using clear criteria, rather than simply including as many disorders as possible. For a particular disorder to be included in carrier screening, the following criteria should be met:

1. **Disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction.**

   a. **The inclusion of disorders characterized by variable expressivity or incomplete penetrance and those known to be associated with a mild phenotype should be optional and made transparent when using these technologies for screening. This recommendation is guided by the ethical principle of nonmaleficence.**

2. **When adult-onset disorders (disorders that could affect offspring of the individual undergoing carrier screening once offspring reach adult life) are included in screening panels, patients must provide consent to screening for these conditions, especially when there may be implications for the health of the individual being screened or for other family member/enrollees.**

a. **This recommendation follows the ethical principles of autonomy and nonmaleficence.**

3. **For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed.**

    a. **Laboratories should specify in their marketing literature and test results how residual risk was calculated using pan-ethnic population data or a specific race/ethnic group.**

    b. **The calculation of residual risk requires knowledge of 2 factors: one is the carrier frequency within a population, the other is the proportion of disease-causing alleles detected using the specific testing platform. Laboratories using multiplex platforms often have limited knowledge of one or both factors. Laboratories offering expanded carrier screening should keep data prospectively and regularly report findings that allow computation of residual risk estimates for all disorders being offered. When data are inadequate, patient materials must stress that negative results should not be overinterpreted.**

4. **There must be validated clinical association between the mutation(s) detected and the severity of the disorder.**

    a. **Patient and provider materials must include specific citations that support inclusion of the mutations for which screening is being performed.**

5. **Compliance with the American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories, including quality control and proficiency testing.**

    a. **Quality control should include the entire test process, including preanalytical, analytical, and post analytical phases. Test performance characteristics should be available to patients and providers accessing testing."**

Cystic Fibrosis Carrier Screening

In 2001, ACMG made the following recommendation:

1. **The Committee recommends that CF carrier screening be offered to non-Jewish Caucasians and Ashkenazi Jews, and made available to other ethnic and racial groups who will be informed of their detectability through educational brochures, the informed consent process, and/or other efficient methods. For example, Asian-Americans and Native-Americans without significant Caucasian admixture should be informed of the rarity of the disease and the very low yield of the test in their respective populations. Testing should be made available to African-Americans, recognizing that only about 50% of at-risk couples will be detected. An educational brochure and a consent form which recites this information as well as a sign-off for those choosing not to be tested after reading these materials is being prepared by the Working Group on Patient Education and Informed Consent.**

2. **We recommend that preconception testing be encouraged whenever possible, although we recognize that for practical purposes, testing will often occur in the prenatal setting."**

In 2020, ACMG released technical standards for *CFTR* variant testing based on available technologies and expanding phenotypic knowledge of rare variants:

> **"The development of the ACMG-23 variant panel followed a careful analysis and revision of the original ACMG-25 variant panel, which was a product of two National Institutes of Health (NIH) consensus conferences (1997 and 1998), followed by a Steering Committee made up of ACMG and ACOG representatives. This was the first time professional organizations recommended population-based screening at the DNA level for a genetic condition.**
> **However, along with advances in technology, the past two decades have brought about an improved understanding of genetics and genomics. As a result, (1) the system of variant classification has been refined, (2) the phenotypes associated with CF (both classic and nonclassic forms) have been better characterized, (3) the associations of CFTR variants with clinically relevant non classic CF phenotypes are now recognized, (4) in vitro genotype–phenotype functional variant analysis exists, and (5) pan-ethnic screening with minimal variation in implementation is accepted. Expanded carrier screening by NGS now makes it possible to screen for clinically relevant variants without regard to ethnicity. The bottleneck is no longer the number of detectable variants but instead an improved understanding of genotype–phenotype correlation."**

Fragile X Syndrome Carrier Screening

ACMG published practice guidelines for carrier screening for Fragile X syndrome (2005), which recommended that Fragile X syndrome carrier testing should be offered to individuals with the following:

- **Individuals seeking reproductive counseling who have (a) a family history of fragile X syndrome or (b) a family history of undiagnosed mental retardation.**

- **Women who are experiencing reproductive or fertility problems associated with elevated follicle stimulating hormone (FSH) levels, especially if they have (a) a family history of premature ovarian failure, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation.**

Ashkenazi Jewish Carrier Panel Testing

ACMG and ACOG published practice guidelines for carrier screening in individuals of Ashkenazi Jewish descent (2008) which made the following recommendations:

> **"We recommend that carrier screening for cystic fibrosis, Canavan disease, familial dysautonomia, and Tay-Sachs disease be offered to all Ashkenazi Jews who are pregnant or considering pregnancy, according to current American College of Medical Genetics and/or the American College of Obstetricians and Gynecologists (ACOG) guidelines. In addition, we recommend that carrier screening be offered for Fanconi anemia (Group C), Niemann-Pick (Type A), Bloom syndrome, mucolipidosis IV, and Gaucher disease.Carrier screening for these disorders should include testing for the specific mutations listed [in Table 1], which will result in a**

carrier detection rate 95% for most disorders. As a result, even in disorders that are relatively less common, expected mutation-specific carrier frequencies are relatively high."

"If only one member of a couple is of Ashkenazi Jewish background, testing should still be offered. Ideally, the Jewish member of the couple should be tested first. If the Jewish partner has a positive test result, the other partner (regardless of background) should be screened for that particular disorder. In the case of Tay-Sachs disease, testing can be performed using the biochemical assay, which has an excellent detection rate regardless of ethnic or racial background. The mutation detection rate and carrier frequency among different ethnic/racial groups is known for cystic fibrosis; however, for the other disorders, a discussion should include the lack of a precise residual risk in the case where the non-Jewish partner is negative on mutation analysis."

"Generally, individuals self-identify themselves as Jewish and whether or not they are of eastern European origin. One Jewish grandparent is sufficient to offer testing. However, if someone is unsure as to their precise lineage, it is recommended to offer testing. At this time, there is no specific panel of tests available for Jews from non-Ashkenazi background. However, a proper family history and ethnic origin should still be obtained and appropriate testing offered (e.g., hemoglobinopathy screening for those from the Mediterranean basin)."

"In the case where someone is identified as a carrier, genetic counseling should be readily available to discuss the findings and possible reproductive options. Furthermore, a discussion regarding the importance of genetic counseling for other family member should be stressed. Although the provider can not contact family member directly, the individual should be encouraged to discuss the findings with his or her family if possible and appropriate"

American College of Obstetricians and Gynecologists (ACOG):

Expanded Carrier Screening Panels

ACOG published practice bulletin No. 690 (2017, reaffirmed 2020) regarding "Carrier Screening in the Age of Genomic Medicine", which made the following recommendations:

- **"Ethnic-specific, panethnic, 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."**
- **"If a patient requests a screening strategy other than the one used by the obstetrician–gynecologist or other health care provider, the requested test should be made available to her after counseling on its limitations, benefits, and alternatives."**
- **"All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and screening for thalassemias and hemoglobinopathies. 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, or women with**

a personal history of ovarian insufficiency. Additional screening also may be indicated based on family history or specific ethnicity."

- **"Couples with consanguinity should be offered genetic counseling to discuss the increased risk of recessive conditions being expressed in their offspring and the limitations and benefits of carrier screening."**
- **"Carrier screening will not identify all individuals who are at risk of the screened conditions. Patients should be counseled regarding residual risk with any test result."**
- **"Prenatal carrier screening does not replace newborn screening, nor does newborn screening diminish the potential benefit of prenatal carrier screening."**
- **"If a woman is found to be a carrier for a specific condition, her reproductive partner should be offered screening to provide accurate genetic counseling for the couple with regard to the risk of having an affected child. Additional genetic counseling should be provided to discuss the specific condition, residual risk, and options for prenatal testing."**
- **"If a carrier couple (ie, carriers for the same condition) is identified before pregnancy, genetic counseling is encouraged so that reproductive options (eg, donor gametes, preimplantation genetic diagnosis, prenatal diagnosis) can be discussed."**
- **"Individuals with a family history of a genetic disorder may benefit from the identification of the specific familial mutation or mutations rather than carrier screening. Knowledge of the specific familial mutation may allow for more specific and rapid prenatal diagnosis."**
- **"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 published practice bulletin No. 691 (March 2017, reaffirmed 2020) and following recommendations related to carrier screening for genetic conditions:

General Recommendations

- **"Information about genetic carrier screening should be provided to every pregnant woman. After counseling, a patient may decline any or all screening."**
- **"Carrier screening and counseling ideally should be performed before pregnancy."**
- **"If an individual is found to be a carrier for a specific condition, the individual's reproductive partner should be offered testing in order to receive informed genetic counseling about potential reproductive outcomes. Concurrent screening of the patient and her partner is suggested if there are time constraints for decisions about prenatal diagnostic evaluation."**

- **"If both partners are found to be carriers of a genetic condition, genetic counseling should be offered. Prenatal diagnosis and advanced reproductive technologies to decrease the risk of an affected offspring should be discussed."**
- **"When an individual is found to be a carrier for a genetic condition, the individual's relatives are at risk of carrying the same mutation. The patient should be encouraged to inform his or her relatives of the risk and the availability of carrier screening. The obstetrician-gynecologist or other healthcare provider should not disclose this information without permission from the patient."**
- **"Carrier screening for a particular condition generally should be performed only once in a person's lifetime, and the results should be documented in the patient's health record. Because of the rapid evolution of genetic testing, additional mutations may be included in newer screening panels. The decision to rescreen a patient should be undertaken only with the guidance of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations."**

Cystic Fibrosis

- **"Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant."**
- **"Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening."**
- **"For couples in which both partners are unaffected but one or both has a family history of cystic fibrosis, genetic counseling and medical record review should be performed to determine if CFTR mutation analysis in the affected family member is available."**
- **"If a woman's reproductive partner has cystic fibrosis or apparently isolated congenital bilateral absence of the vas deferens, the couple should be provided follow-up genetic counseling by an obstetrician–gynecologist or other health care provider with expertise in genetics for mutation analysis and consultation."**

Spinal Muscular Atrophy

- **"Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant."**

Fragile X Syndrome

- **"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."**
- **"All identified individuals with intermediate results and carriers of a fragile X premutation or full mutation should be provided follow-up genetic counseling to discuss the risk to their offspring of inheriting an expanded full-mutation fragile X allele and to discuss fragile X-associated disorders (premature ovarian insufficiency and fragile X tremor/ataxia syndrome)."**

Hemoglobinopathies

- **"A complete blood count with red blood cell indices should be performed in all women who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of a hemoglobinopathy. Ideally, this testing also should be offered to women before pregnancy."**
- **"A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent). If red blood cell indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume, hemoglobin electro- phoresis also should be performed."**

Ashkenazi Jewish Carrier Screening

- **"When only one partner is of Ashkenazi Jewish descent, that individual should be offered screening first. If it is determined that this individual is a carrier, the other partner should be offered screen- ing. However, the couple should be informed that the carrier frequency and the detection rate in non-Jewish individuals are unknown for most of these disorders, except for Tay–Sachs disease and cystic fibrosis. Therefore, it is difficult to accurately predict the couple's risk of having a child with the disorder."**

National Society of Genetic Counselors (NSGC):

Expanded Carrier Screening Panels

The National Society of Genetic Counselors released a position statement (2017) endorsing the use of multi-gene panels when clinically warranted and appropriately applied, stating the following:

> **"These tests can provide a comprehensive and efficient route to identifying the genetic causes of disease. Before ordering a multi-gene panel test, providers should thoroughly evaluate the analytic and clinical validity of the test, as well as its clinical utility. Additional factors to consider include, but are not limited to: clinical and family history information, gene content of the panel, limitations of the sequencing and informatics technologies, and variant interpretation and reporting practices. Panels magnify the complexities of genetic testing and underscore the value of experts, such as genetic counselors, who can educate stakeholders about appropriate utilization of the technology to mitigate risks of patient harm and unnecessary costs to the healthcare system. NSGC supports straightforward and transparent pricing so that patients, providers, laboratories, and health plans can easily weigh the value of genetic testing in light of its cost."**

The National Society of Genetic Counselors updated a position statement (2017) regarding the genetic testing of minors for adult-onset conditions, stating the following:

> **"[NSGC] encourages deferring predictive genetic testing of minors for adult-onset conditions when results will not impact childhood medical management or significantly benefit the child. Predictive testing should optimally be deferred until the individual has the capacity to weigh the associated risks, benefits, and limitations of this information, taking his/her circumstances, preferences, and beliefs into account to preserve his/her autonomy and right to an open future."**

European Molecular Genetics Quality Network (EMQN)

Duchenne and Becker Muscular Dystrophy Carrier Screening

EMQN published best practice guidelines for genetic testing in dystrophinopathies (2020), which included the following in regard to carrier testing in females:

> **"When the familial pathogenic variant is known, carrier testing should be undertaken by specific testing for this variant."**
>
> **"When the familial pathogenic variant is unknown and an affected male is not available to be tested, female relatives at risk of being carriers should be offered the full cohort of level 1 and 2 genetic testing (i.e. CNV analysis and sequencing) since these two approaches are cost effective and offer ~99% sensitivity."**

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2021, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Rebranded from corporate policy	8/22	

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading

national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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