GENETIC TESTING: PRENATAL AND PRECONCEPTION CARRIER SCREENING

OVERVIEW

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.

POLICY REFERENCE TABLE

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

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Expanded Carrier Screening Panels	Foresight Carrier Screen (Myriad) Inheritest 500 Plus Panel (LabCorp) GeneSeq (LabCorp) Comprehensive Carrier Screening (Invitae) Comprehensive Carrier Screen without X-linked Disorders (Invitae) Broad Carrier Screen (Invitae) Broad Carrier Screen without X-linked Disorders (Invitae)	81443	O09, Z13, Z31, Z34, Z36, Z84	4, 6, 7
	Inheritest Comprehensive Panel (Labcorp)	81243, 81329, 81443		
	Horizon 14 (Natera) Horizon 27 (Natera) Horizon 274 (Natera)	81243, 81257, 81329, 81443		
Basic Carrier Screening Panels (Cystic Fibrosis, Spinal Muscular Atrophy, Fragile X, Hemoglobinopathies but not more than 14 genes)	Inheritest Core Panel (LabCorp) Inheritest Carrier Screen, Society-guided Panel (14 Genes) (LabCorp) Prenatal Carrier Panel (Quest Diagnostics) Foresight Fundamental Panel (Myriad) Core Carrier Screen (Invitae)	81220, 81329, 81243	O09, Z13, Z31, Z34, Z36, Z84	
Cystic Fibrosis Carrier Screening				
CFTR Known Familial Variant Analysis	Targeted Variants: CFTR (PreventionGenetics)	81221	O09, Z13, Z31, Z36, Z83.49	1, 2, 4, 12
CFTR Sequencing and/or Deletion/Duplication	Cystic Fibrosis Complete Rare Variant Analysis, Entire Gene Sequence (Quest Diagnostics)	81223		

Analysis, or Mutation Panel	Cystic Fibrosis Gene Deletion or Duplication (Quest Diagnostics)	81222		
	Cystic Fibrosis (CF) Profile, 32 mutations, DNA Analysis (LabCorp) Cystic Fibrosis Screen (Quest Diagnostics)	81220		
CFTR Intron 9 PolyT and TG Analysis (aka Intron 8 poly-T/TG)	*CFTR* Intron 8 Poly-T Analysis (Quest Diagnostics)	81224		
Spinal Muscular Atrophy Carrier Screening				
SMN1 Targeted Variant Analysis	Known Variant Testing-SMN1 (Nemours) SMN1 Targeted Variant - 2 Variants Test (GeneDx)	81337	O09, Z13, Z31, Z34, Z36, Z84	5, 9
SMN1 Sequencing and/or Deletion/Duplication Analysis	Spinal Muscular Atrophy Carrier Test (Natera)	81329		
Fragile X Syndrome Carrier Screening				
FMR1 Repeat Analysis	Fragile X Syndrome, PCR with Reflex to Southern Blot (LabCorp)	81243	O09, Z13, Z31, Z34, Z36, Z84	5, 11
	Fragile X Syndrome, PCR and Southern Blot Analysis (LabCorp)	81243, 81244		
Hemoglobinopathy Carrier Screening				
HBA1, *HBA2*, or *HBB* Targeted Variant Analysis	Alpha-Globin Common Mutation Analysis (Quest Diagnostics)	81257	O09, Z13, Z31, Z34, Z36, Z84	5
	HBA1 Targeted Variant-Single Test (GeneDx) *HBA2* Targeted Variant-Single Test (GeneDx)	81479		
	Targeted Variant-HBB (PreventionGenetics)	81362		
HBA1, *HBA2*, or *HBB* Sequencing and/or Deletion/Duplication Analysis	Alpha-Globin Gene Sequencing (Quest Diagnostics)	81259		
	HBA1 Deletion/Duplication (GeneDx)	81479		

	HBA2 Deletion/Duplication (GeneDx)			
	HBB Carrier-Full Gene Sequencing and Deletion/Duplication (Invitae)	81363, 81364		
Ashkenazi Jewish Carrier Panel Testing				
Ashkenazi Jewish Carrier Panel Testing	Ashkenazi Jewish Panel (Quest Diagnostics)	81412	O09, Z13, Z31, Z34, Z36, Z84	5, 8
Duchenne and Becker Muscular Dystrophy Carrier Screening				
DMD Targeted Variant Analysis	Targeted Variants-DMD (PreventionGenetics)	81403	O09, Z13, Z31, Z34, Z36, Z84	10
DMD Sequencing and/or Deletion/Duplication Analysis	Duchenne/Becker MD (DMD) Gene Sequencing (GeneDx)	81408		
	Duchenne/Becker MD (DMD) Del/Dup (GeneDx)	81161		
	Genomic Unity DMD Gene Analysis (Variantyx)	0218U		
General Criteria for Targeted Carrier Screening				
General Criteria for Targeted Carrier Screening	Varies	81174, 81190, 81200, 81205, 81209, 81242, 81247, 81248, 81250, 81251, 81253, 81254, 81289, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408	Z14, Z15, Z31	3, 4, 5

OTHER RELATED POLICIES

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

- ***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.
- ***Genetic Testing: Noninvasive Prenatal Screening (NIPS)*** for coverage criteria related to prenatal cell-free DNA screening tests.
- ***Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability and Developmental Delay*** for coverage criteria related to suspected multisystem genetic conditions in the postnatal period.
- ***Genetic Testing: Hearing Loss*** for coverage related to diagnostic genetic testing for hereditary hearing loss.
- ***Genetic Testing: Hematologic Conditions (non-cancerous)*** for coverage related to diagnostic genetic testing for alpha-thalassemia and other hemoglobinopathies.
- ***Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for coverage related to diagnostic genetic testing for mitochondrial and other disorders.
- ***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.

COVERAGE CRITERIA

EXPANDED CARRIER SCREENING PANELS

I. Expanded carrier screening panels (81243, 81257, 81329, 81443*) may be considered **medically necessary** when:

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

   B. The panel includes the genes *CFTR* and *SMN1*.

II. Expanded carrier screening panels (81243, 81257, 81329, 81443*) are considered **investigational** for all other indications.

*Fragile X (81243) and spinal muscular atrophy (SMA) (81329) carrier screening may be billed along with 81443 if performed separately from the remainder of the panel per CPT Code Book Guidelines.

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BASIC CARRIER SCREENING PANELS (CYSTIC FIBROSIS, SPINAL MUSCULAR ATROPHY, FRAGILE X, HEMOGLOBINOPATHIES)

Basic carrier screening panels (*CFTR, SMN1/2, FMR1, HBB/HBA1/HBA2*) (81220, 81329, 81243) should be evaluated not as a panel, but by the individual test criteria described below.

I. Cystic fibrosis carrier screening
II. Spinal muscular atrophy carrier screening
III. Fragile X syndrome carrier screening
IV. Hemoglobinopathy carrier screening

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CYSTIC FIBROSIS CARRIER SCREENING

CFTR Known Familial Variant Analysis

I. Cystic fibrosis carrier screening via *CFTR* targeted mutation analysis for a known familial mutation (81221) may be considered **medically necessary** when:

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

   B. The member has a close relative with a known pathogenic or likely pathogenic variant in *CFTR*.

II. Cystic fibrosis carrier screening via *CFTR* targeted mutation analysis for a known familial mutation (81221) is considered **investigational** for all other indications.

CFTR Sequencing, Deletion/Duplication Analysis, or Mutation Panel

I. Cystic fibrosis carrier screening via *CFTR* sequencing (81223), deletion/duplication analysis (81222), or a mutation panel (81220) using at a minimum the ACMG-23 variant panel, may be considered **medically necessary** when:

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

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

II. Cystic fibrosis carrier screening via *CFTR* sequencing (81223), deletion/duplication analysis (81222), or a mutation panel (81220) using at a minimum the ACMG-23 variant panel, is considered **investigational** for all other indications.

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

I. Analysis of the *CFTR* intron 9 polyT and TG regions (81224) for cystic fibrosis carrier screening may be considered **medically necessary** when:

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

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

II. Analysis of the *CFTR* intron 9 polyT and TG regions (81224) for cystic fibrosis carrier screening is considered **investigational** for all other indications.

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

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SPINAL MUSCULAR ATROPHY CARRIER SCREENING

SMN1 Targeted Variant Analysis

I. Spinal muscular atrophy (SMA) carrier screening via *SMN1* targeted variant analysis (81337) may be considered **medically necessary** when:

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

   B. The member has a close relative with a known pathogenic or likely pathogenic variant in *SMN1*.

II. Spinal muscular atrophy (SMA) carrier screening via *SMN1* targeted variant analysis (81337) is considered **investigational** for all other indications.

SMN1 Sequencing and/or Deletion/Duplication Analysis

I. Spinal muscular atrophy (SMA) carrier screening via *SMN1* sequencing and/or deletion/duplication analysis (81329) is considered **medically necessary** when:

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

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

II. Spinal muscular atrophy (SMA) carrier screening via *SMN1* sequencing and/or deletion/duplication analysis (81329) is considered **investigational** for all other indications.

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

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FRAGILE X SYNDROME CARRIER SCREENING

FMR1 Repeat Analysis

I. Fragile X carrier screening via *FMR1* CGG-trinucleotide repeat analysis (81243, 81244) may be considered **medically necessary** when:

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

   B. The member is considering a pregnancy or is currently pregnant, **AND**

      1. The member has one of the following:

         a) Close relative with Fragile X syndrome (i.e., close relative has more than 200 CGG repeats in the *FMR1* gene), **OR**

         b) Close relative who is a known carrier for Fragile X syndrome (i.e., close relative has between 55-200 CGG repeats in the *FMR1* gene), **OR**

         c) Close relative with unexplained intellectual disability, developmental delay, or autism spectrum disorder, **OR**

         d) Close relative diagnosed with premature ovarian insufficiency or elevated follicle-stimulating hormone level before age 40 years.

II. Fragile X carrier screening via *FMR1* CGG-trinucleotide repeat analysis (81243, 81244) is considered **investigational** for all other indications.

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

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HEMOGLOBINOPATHY CARRIER SCREENING

HBA1, *HBA2*, or *HBB* Targeted Variant Analysis

I. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81257, 81479), or *HBB* (81362) targeted variant analysis may be considered **medically necessary** when:

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

   B. The member meets one of the following:

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

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

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

      4. The member'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. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81257, 81479), or *HBB* (81362) targeted variant analysis is considered **investigational** for all other indications.

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

I. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81259, 81479), or *HBB* (81363, 81364) sequencing and/or deletion/duplication analysis may be considered medically necessary when:

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

   B. The member meets one of the following:

      1. The member'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. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81259, 81479), or *HBB* (81363, 81364) sequencing and/or duplication analysis is considered **investigational** for all other indications.

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

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ASHKENAZI JEWISH CARRIER PANEL TESTING

I. Ashkenazi Jewish carrier panel testing (81412) may be considered **medically necessary** when:

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

B. The member is of Ashkenazi Jewish ancestry, **AND**

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.

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DUCHENNE AND BECKER MUSCULAR DYSTROPHY CARRIER SCREENING

DMD Targeted Variant Analysis

I. Duchenne and Becker muscular dystrophy carrier screening via *DMD* targeted variant analysis (81403) may be considered **medically necessary** when:

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

   B. The member has a close relative with a known pathogenic or likely pathogenic variant in *DMD*.

II. Duchenne and Becker muscular dystrophy carrier screening via *DMD* targeted variant analysis (81403) is considered **investigational** for all other indications.

DMD Sequencing and/or Deletion/Duplication Analysis

I. Duchenne and Becker muscular dystrophy carrier screening via *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) may be considered **medically necessary** when:

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

B. The member has one of the following:

1. First- or second-degree male relative diagnosed with Duchenne or Becker muscular dystrophy.

II. Duchenne and Becker muscular dystrophy carrier screening via *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) is considered **investigational** for all other indications.

Note: Refer to *Genetic Testing for Epilepsy, Neuromuscular, and Neurodegenerative Disorders* for coverage criteria for genetic testing to establish a diagnosis of Duchenne or Becker muscular dystrophy.

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GENERAL CRITERIA FOR CARRIER SCREENING

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

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

B. The genetic disorder is a recessive condition with a childhood onset, **AND**

C. One of the following:

1. The member has a close relative with a known pathogenic or likely pathogenic variant associated with the disorder, **OR**

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

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

4. The member or the member's reproductive partner has a first- or second-degree relative who is affected with the genetic disorder.

II. 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) is considered **investigational** when the member does not meet any criteria above.

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NOTES AND DEFINITIONS

1. **Close relatives** include first, second, and third degree relatives on the same side of the family:

   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.

CLINICAL CONSIDERATIONS

"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-Canadian, 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 AND RATIONALE

Expanded Carrier Screening Panels

American College of Obstetricians and Gynecologists (ACOG)

The American College of Obstetricians and Gynecologists (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." (page e95) It was also recommended that: "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." (page e95)

American College of Medical Genetics and Genomics (ACMG), American College of Obstetricians and Gynecologists (ACOG), the National Society of Genetic Counselors (NSGC), the Perinatal Quality Foundation, and the Society of Maternal-Fetal Medicine (SMFM)

The American College of Medical Genetics and Genomics (ACMG), ACOG, the National Society of Genetic Counselors (NSGC), the Perinatal Quality Foundation, and the Society

of Maternal-Fetal Medicine (SMFM) published a commentary discussing expanded carrier screening in 2015 stating that "...women of reproductive age should ideally be offered carrier screening before conception." (page 657)

American College of Medical Genetics and Genomics (ACMG)

ACMG published a practice resource (2021) regarding screening for autosomal recessive and X-linked conditions during pregnancy and preconception, which includes 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 or more common carrier frequency (includes Tier 1)
    - Tier 3: 1/200 or more common carrier frequency (includes Tier 2) includes X-linked conditions
    - Tier 4: Less than 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.
- Reproductive partners of pregnant patients and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions when carrier screening is performed simultaneously with their partner."

ACMG does not recommend:

- Offering Tier 1 and/or Tier 2 screening without Tier 3, because these do not provide equitable evaluation of all racial/ethnic groups.
- Routine offering of Tier 4 panels.

Cystic Fibrosis Carrier Screening

National Society of Genetic Counselors (NSGC)

NSGC published recommendations in 2013 addressing carrier screening for cystic fibrosis. It is recommended that: "Carrier testing for CF [cystic fibrosis] should be offered to all women of reproductive age, regardless of ancestry; preferably pre-conceptionally. CF carrier testing should also be offered…to partners of mutation carriers…" (page 8)

American College of Obstetricians and Gynecologists (ACOG)

The American College of Obstetricians and Gynecologists (ACOG) published practice bulletin No. 690 (2017, reaffirmed 2020) regarding "Carrier Screening in the Age of Genomic Medicine", which made the following recommendations for cystic fibrosis carrier screening:

- 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.

American College of Medical Genetics and Genomics (ACMG)

In 2001, ACMG made the following recommendation (Grody et al, 2001):

- 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.

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

- The Committee recommends that the R117H mutation be included in the test panel, while recognizing that this will screen for male infertility as well as CF. Thus, to distinguish the genotypes of R117H associated with CF from that associated with CBAVD, reflex testing for the 5T/7T/9T variant is recommended only when the R117H mutation is positive.

In their 2020 technical standard for *CFTR* variant testing, the American College of Medical Genetics and Genomics (ACMG) recommends a minimum number of mutations tested in the *CFTR* gene if carrier testing is pursued: "For those laboratories who wish to continue using a targeted testing approach, the ACMG-23 variant panel remains as the minimum list of CFTR variants that should be included." (page 5)

> "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.

Spinal Muscular Atrophy Carrier Screening

American College of Obstetricians and Gynecologists (ACOG)

The American College of Obstetricians and Gynecologists (ACOG) published practice bulletin No. 691 (March 2017, reaffirmed 2020) and following recommendation:

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

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics recommended the following on carrier screening for spinal muscular atrophy (Prior, et al, 2008):

Because SMA is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity. Ideally, the testing should be offered before conception or early in pregnancy. The primary goal is to allow carriers to make informed reproductive choices.

Fragile X Syndrome Carrier Screening

American College of Obstetricians and Gynecologists (ACOG)

The American College of Obstetricians and Gynecologists (ACOG) published practice bulletin No. 691 (2017) regarding “Carrier Screening for Genetic Conditions”, which made the following recommendations:

- 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 (p. 598).
- 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 (p. 598).
- 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) (p. 598).

- Prenatal diagnostic testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation (p. 598).
- DNA-based molecular analysis (eg, Southern blot analysis and polymerase chain reaction) is the preferred method of diagnosis of fragile X syndrome and of determining *FMR1* triplet repeat number (eg, premutations). In rare cases, the size of the triplet repeat and the methylation status do not correlate, which makes it difficult to predict the clinical phenotype. In cases of this discordance, the patient should be referred to a genetics professional (p. 599).

American College of Medical Genetics and Genomics (ACMG)

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 (p. 586).

- 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 (p. 586).

Hemoglobinopathies

American College of Obstetricians and Gynecologists (ACOG)

ACOG published practice bulletin No. 691 (March 2017, reaffirmed 2020) and following recommendations related to carrier screening:

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

Ashkenazi Jewish Carrier Panel Testing

American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics and Genomics (ACMG)

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 members should be stressed. Although the provider cannot contact

> family members 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)

ACOG published practice bulletin No. 691 (March 2017, reaffirmed 2020) and following recommendations related to 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 screening. 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.

Duchenne and Becker Muscular Dystrophy Carrier Screening

European Molecular Genetics Quality Network (EMQN)

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.

General Criteria for Targeted Carrier Screening

American College of Obstetricians and Gynecologists (ACOG)

ACOG published practice bulletin No. 691 (March 2017, reaffirmed 2020) and following recommendations related to carrier screening:

- Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth.
- Carrier screening panels should not include conditions primarily associated with a disease of adult onset.

ACOG published practice bulletin No. 690 (March 2017) and following recommendations related to carrier screening

- Carrier screening is a term used to describe genetic testing that is performed on an individual who does not have any overt phenotype for a genetic disorder but may have one variant allele within a gene(s) associated with a diagnosis.
- Information about carrier screening should be provided to every pregnant woman.
- Carrier screening and counseling ideally should be performed before pregnancy because this enables couples to learn about their reproductive risk and consider the most complete range of reproductive options. A patient may decline any or all screening.
- When an individual is found to be a carrier for a genetic condition, his or her 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.
- If an individual is found to be a carrier for a specific condition, the patient's reproductive partner should be offered testing in order to receive informed genetic counseling about potential reproductive outcomes.
- If both partners are found to be carriers of a genetic condition, genetic counseling should be offered.

National Society of Genetic Counselors (NSGC):

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.

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