

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. The majority of professional societies recommend carrier screening prior to pregnancy. 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.

“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.

POLICY REFERENCE TABLE

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the [Concert Genetics Platform](#) for a comprehensive list of registered tests

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Expanded Carrier Screening Panels	Foresight Universal Panel Carrier Screen (Myriad Genetics)	81329, 81443	O09, Z13, Z31, Z34, Z36, Z84	2, 4
	Inheritest 500 Plus Panel (Labcorp) Comprehensive Carrier Screening (Invitae)	81443		
	GeneSeq Plus (Labcorp)	81336, 81405, 81408, 81479		
	QHerit™ Expanded Carrier Screen (Quest Diagnostics)	81243, 81443		
	Horizon 27 (Natera)	81243, 81257, 81329, 81443		
Basic Carrier Screening Panels (Cystic Fibrosis, Spinal Muscular Atrophy, Fragile X, Hemoglobinopathies, not more than 14 genes)	Inheritest Core Panel (Labcorp)	81220, 81222, 81223, 81243, 81257, 81329, 81336	O09, Z13, Z31, Z34, Z36, Z84	2, 3
	Inheritest Carrier Screen, Society-guided Panel (14 Genes) (Labcorp)			
	Prenatal Carrier Panel (Quest)			

	Diagnosics)			
	Foresight Fundamental Panel (Myriad Genetics)			
	Core Carrier Screen (Invitae)			
<u>Cystic Fibrosis Carrier Screening</u>				
CFTR Known Familial Variant Analysis	CFTR Targeted Variants - Single Test (GeneDx)	81221	O09, Z13, Z31, Z36, Z83.49	3
CFTR Sequencing and/or Deletion/Duplication Analysis, or Mutation Panel	Cystic Fibrosis Complete Rare Variant Analysis, Entire Gene Sequence (Quest Diagnostics)	81223		1
	Cystic Fibrosis Gene Deletion or Duplication (Quest Diagnostics)	81222		
	CFvantage Cystic Fibrosis Expanded Screen (Quest Diagnostics)	81220		
CFTR Intron 9 PolyT and TG Analysis (previously called Intron 8 polyT/TG Analysis)	CFTR Intron 8 Poly-T Analysis (Quest Diagnostics)	81224		
<u>Spinal Muscular Atrophy Carrier Screening</u>				
SMN1 Targeted Variant Analysis	Spinal Muscular Atrophy - SMN1 Known Variant Testing (Nemours) SMN1 Targeted Variant - 2 Variants Test (GeneDx)	81337, 81403	O09, Z13, Z31, Z34, Z36, Z84	3
SMN1 Sequencing and/or Deletion/Duplication and SMN2 Deletion/Duplication Analysis	Spinal Muscular Atrophy Carrier Test (Natera)	81329, 81336, 81401, 81405		3, 5
	Genomic Unity SMN1/2 Analysis (Variantyx Inc)	0236U		
<u>Fragile X Syndrome Carrier Screening</u>				
FMR1 Repeat Analysis	Fragile X Syndrome, PCR with Reflex to Southern Blot (Integrated)	81243, 81244	O09, Z13, Z31, Z34,	3, 8, 9

	Genetics)		Z36, Z84	
	Fragile X Syndrome, PCR and Southern Blot Analysis (Labcorp)			
<u>Hemoglobinopathy Carrier Screening</u>				
<u>HBA1, HBA2, or HBB Targeted Variant Analysis</u>	Alpha-Globin Common Mutation Analysis (Quest Diagnostics)	81257, 81258	O09, Z13, Z31, Z34, Z36, Z84	3
	HBA1 Targeted Variant-Single Test (GeneDx) HBA2 Targeted Variant-Single Test (GeneDx)			
	HBB Targeted Variant - Single Test (GeneDx)	81361, 81362		
<u>HBA1, HBA2, or HBB Sequencing and/or Deletion/Duplication Analysis</u>	Alpha-Globin Gene Sequencing and Deletion/Duplication (Quest Diagnostics)	81259, 81269, 81363, 81364		
	HBA1 Deletion/Duplication (GeneDx) HBA2 Deletion/Duplication (GeneDx)			
	HBB Carrier-Full Gene Sequencing and Deletion/Duplication (Invitae)			
<u>Ashkenazi Jewish Carrier Panel Testing</u>				
<u>Ashkenazi Jewish Carrier Panel Testing</u>	Ashkenazi Jewish Panel (11 Tests) (Quest Diagnostics)	81412	O09, Z13, Z31, Z34, Z36, Z84	3
<u>Duchenne and Becker Muscular Dystrophy Carrier Screening</u>				
<u>DMD Targeted Variant Analysis</u>	DMD Targeted Variants - Single Test (GeneDx)	814793	O09, Z13, Z31, Z34, Z36, Z84	6
<u>DMD Sequencing and/or Deletion/Duplication Analysis</u>	Duchenne/Becker MD (DMD) Gene Sequencing (GeneDx)	81161, 81408		7
	Duchenne/Becker MD (DMD) Del/Dup (GeneDx)			
	Genomic Unity DMD Gene Analysis (Variantyx)	0218U		
<u>General Criteria for Targeted Carrier Screening</u>				

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	2, 3
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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 and Molecular 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, 81336, 81405, 81408, 81479, 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, 81336, 81405, 81408, 81479, 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.

**ACMG recommends follow-up screening for the partner of the member that is pregnant or considering pregnancy via analysis of the same gene that has the pathogenic or LP variant as identified in the member. Therefore, expanded carrier screening panels are not recommended to be completed by both reproductive partners in tandem.

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BASIC CARRIER SCREENING PANELS (Cystic fibrosis, Spinal Muscular Atrophy, Fragile X, Hemoglobinopathies, not more than 14 genes)

- I. Basic carrier screening panels (*CFTR*, *SMN1/2*, *FMR1*, *HBB/HBA1/HBA2*, but not more than 14 genes) (81220, 81222, 81223, 81243, 81257, 81329, 81336) 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. Basic carrier screening panels (*CFTR*, *SMN1/2*, *FMR1*, *HBB/HBA1/HBA2*, but not more than 14 genes) (81220, 81222, 81223, 81329, 81243, 81257, 81329, 81336) are considered investigational for all other indications.

*ACMG recommends follow-up screening for the partner of the member that is pregnant or considering pregnancy via analysis of the same gene that has the pathogenic or LP variant as identified in the member. Therefore, basic carrier screening panels are not recommended to be completed by both reproductive partners in tandem.

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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, 81403) 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, 81403) is considered **investigational** for all other indications.

SMN1 Sequencing and/or Deletion/Duplication and SMN2 Deletion/Duplication Analysis

- I. Spinal muscular atrophy (SMA) carrier screening via *SMN1* sequencing and/or deletion/duplication analysis and *SMN2* deletion/duplication analysis (81329, 81336, 81401, 81405, 0236U) 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 and *SMN2* deletion/duplication analysis (81329, 81336, 81401, 81405, 0236U) 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, 81258), or *HBB* (81361, 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 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, 81258), or *HBB* (81361, 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, 81269), 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'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, 81269), 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 type A (SMPD1)
 8. Gaucher disease Type 1 (GBA)
 9. Mucopolidosis IV (MCOLN1)
 10. Glycogen storage disease type I
 11. Joubert syndrome
 12. Maple syrup urine disease

13. Usher syndrome

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 (81479) 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 (81479) 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 a [first- or second-degree](#) 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 TARGETED 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.

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 2023) 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.” (p. e35)

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.” (p. e35)

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 (p. 1796)
 - Tier 1: CF + SMA + Risk Based Screening
 - Tier 2: 1/100 carrier frequency or higher (includes Tier 1)
 - Tier 3: 1/200 carrier frequency or higher (includes Tier 2) includes X-linked conditions
 - Tier 4: 1/200 carrier frequency or higher (includes Tier 3) genes/condition will vary by lab
- All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening. (p. 1797)
- Tier 4 screening should be considered (p. 1797):
 - 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.
- Additionally, ACMG recommends follow-up screening of the partner with analysis of the same gene that has the pathogenic or LP variant as that identified in the partner. (p. 1804)

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. (p. 1797)

Basic Carrier Screening Panels (Cystic Fibrosis, Spinal Muscular Atrophy, Fragile X, Hemoglobinopathies, not more than 14 genes)

American College of Obstetricians and Gynecologists (ACOG)

ACOG published practice bulletin No. 691 (March 2017, reaffirmed 2020), which includes the following recommendations related to carrier screening (p. 598):

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

- Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant.

ACOG published practice bulletin No. 690 (March 2017, reaffirmed 2020), which includes the following recommendations related to carrier screening (p. e35):

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.

CYSTIC FIBROSIS CARRIER SCREENING

***CFTR* Known Familial Analysis**

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

Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant. When 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. Carrier screening should be offered for both partners, with attention to ensure that the familial mutation is included in the assessment. (p. 598)

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

American College of Medical Genetics and Genomics (ACMG)

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.” (p. 5)

The ACMG recommends that laboratories performing initial *CFTR* variant testing on an individual can use either targeted or comprehensive methods to evaluate the gene. If pathogenic or likely pathogenic *CFTR* variants have been confirmed in *both* biological parents, or an affected full sibling, only targeted methods should be used. (p. 7)

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

American College of Medical Genetics and Genomics (ACMG)

In their 2020 technical standard for *CFTR* variant testing, the American College of Medical Genetics and Genomics (ACMG) recommends that, for all prenatal, postnatal, and adult diagnostic testing indications for *CFTR*, the R117H status as well as the results from at least the associated polyT tract be reported. For all adult carrier screening indications for *CFTR*, polyT status should be reported when the R117H variant is detected; laboratories may also want to consider reporting the results from the associated polyT tract in the partner of an individual who had a pathogenic or likely pathogenic variant detected during screening. (p. 12)

SPINAL MUSCULAR ATROPHY CARRIER SCREENING

SMN1 Targeted Variant Analysis

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 (p. 597-598):

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. Individuals with a positive family history of a genetic condition should be offered carrier screening for the specific condition and may benefit from genetic counseling.

SMN1 Sequencing and/or Deletion/Duplication and SMN2 Deletion/Duplication Analysis

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 the following recommendations (p. 598):

- 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. (p. 841)

FRAGILE X SYNDROME CARRIER SCREENING

***FMR1* Repeat Analysis**

American College of Obstetricians and Gynecologists (ACOG)

The American College of Obstetricians and Gynecologists (ACOG) published practice bulletin No. 691 (2017, reaffirmed in 2020) regarding “Carrier Screening for Genetic Conditions”, which made the following recommendations (p. 2):

- 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).
- Prenatal diagnostic testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation.

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.
- 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)

American College of Obstetricians and Gynecologists (ACOG)

ACOG published practice bulletin No. 605 (July 2014, reaffirmed 2021), which states the following:

“If a woman has a personal or family history of ovarian failure or an elevated follicle-stimulating hormone (FSH) level before age 40 years without a known cause, fragile X premutation carrier testing should be offered”. (p. 194)

HEMOGLOBINOPATHY CARRIER SCREENING

HBA1, HBA2, or HBB Targeted Variant Analysis

American College of Obstetricians and Gynecologists (ACOG)

ACOG published practice bulletin No. 691 (March 2017, reaffirmed 2020) and following recommendations related to carrier screening (p. 597):

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. Additionally, when an individual is found to be a carrier of 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. (p. 597)

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

American College of Obstetricians and Gynecologists (ACOG)

ACOG published practice bulletin No. 691 (March 2017, reaffirmed 2020) and following recommendations related to carrier screening (p. 598):

- 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.
- Beta-thalassemia is associated with elevated hemoglobin F and elevated hemoglobin A2 levels [identified on hemoglobin electrophoresis]. (p.9)
- Neither hemoglobin electrophoresis nor solubility testing can identify individuals with alpha-thalassemia trait; only molecular genetic testing can identify this condition. If the mean corpuscular volume is below normal, iron deficiency anemia has been excluded, and the hemoglobin electrophoresis is not consistent with beta-thalassemia trait (ie. there is no elevation of HbA2 or HbF), then DNA-based testing should be used to detect alpha globin gene deletions characteristic of alpha-thalassemia. (p.9)

Ashkenazi Jewish Carrier Panel Testing

American College of Obstetricians and Gynecologists (ACOG) ACOG published practice bulletin No. 691 (2017), which provided carrier screening guidelines in individuals of Eastern and Central European Jewish descent (i.e., Ashkenazi Jewish). Specifically, they made the following recommendations:

- Cystic fibrosis, Canavan disease, familial dysautonomia, and Tay-Sachs disease carrier screening should be offered to all Ashkenazi Jewish individuals who are pregnant or considering pregnancy
- Consider carrier screening for Fanconi anemia (Group C), Niemann-Pick (Type A), Bloom syndrome, mucopolysaccharidosis IV, glycogen storage disease type I, Joubert syndrome, maple syrup urine disease, Usher syndrome, and Gaucher disease. (p. 11-13)

- 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. (p. 3)

DUCHENNE AND BECKER MUSCULAR DYSTROPHY CARRIER SCREENING

DMD Targeted Variant Analysis

GeneReviews: Dystrophinopathies

GeneReviews is an expert-authored review of current literature on a genetic disease and goes through a rigorous editing and peer review process before being published online.

Per GeneReviews, it is appropriate to evaluate at-risk female family members (i.e., the sisters or maternal female relatives of an affected male and first-degree relatives of a known or possible heterozygous female) in order to identify as early as possible heterozygous females who would benefit from cardiac surveillance. Evaluations can include molecular genetic testing if the *DMD* pathogenic variant in the family is known.

DMD Sequencing and/or Deletion/Duplication Analysis

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 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.” (p. 1147)

General Criteria for Targeted Carrier Screening

American College of Obstetricians and Gynecologists (ACOG)

ACOG published practice bulletin No. 690 (March 2017, reaffirmed 2023), which includes the 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. (p. e36)

ACOG published practice bulletin No. 691 (March 2017), which includes the following recommendations related to carrier screening:

- 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. (p. 597)

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REFERENCES

1. Deignan JL, Astbury C, Cutting GR, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2020;22(8):1288-1295. doi:10.1038/s41436-020-0822-5
2. Committee Opinion No. 690 (Reaffirmed 2023: Carrier Screening in the Age of Genomic Medicine. *Obstet Gynecol.* 2017;129(3):e35-e40. doi:10.1097/AOG.0000000000001951
3. Committee Opinion No. 691 Summary: Carrier Screening for Genetic Conditions. *Obstet Gynecol.* 2017 (Reaffirmed 2020);129(3):597-599. doi:10.1097/AOG.0000000000001948
4. Gregg AR, Aarabi M, Klugman S, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG) [published online ahead of print, 2021 Jul 20] [published correction appears in *Genet Med.* 2021 Aug 27;:]. *Genet Med.* 2021;10.1038/s41436-021-01203-z. doi:10.1038/s41436-021-01203-z
5. Prior TW; Professional Practice and Guidelines Committee. Carrier screening for spinal muscular atrophy. *Genet Med.* 2008;10(11):840-842. doi:10.1097/GIM.0b013e318188d069
6. Darras BT, Urion DK, Ghosh PS. Dystrophinopathies. 2000 Sep 5 [Updated 2022 Jan 20]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-20230. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK11119/>
7. Fratter C, Dalgleish R, Allen SK, et al. EMQN best practice guidelines for genetic testing in dystrophinopathies. *Eur J Hum Genet.* 2020;28(9):1141-1159. doi:10.1038/s41431-020-0643-7
8. Sherman S, Pletcher BA, Driscoll DA. Fragile X syndrome: diagnostic and carrier testing. *Genet Med.* 2005;7(8):584-587. doi:10.1097/01.gim.0000182468.22666.dd
9. Committee opinion no. 605: primary ovarian insufficiency in adolescents and young women. *Obstet Gynecol.* 2014;124(1):193-197. doi:10.1097/01.AOG.0000451757.51964.98

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