Medica Coverage Policy

Policy Name:	**Genetic Testing: Prenatal and Preconception Carrier Screening**
Effective Date:	**July 01, 2024**

Important Information – Please Read Before Using This Policy
These services may or may not be covered by all Medica plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between policy requirements and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

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.

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

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)	81443		
	Comprehensive Carrier Screen (Invitae)			
	GeneSeq Plus (Labcorp)	81336, 81405,81408, 81479		
	QHerit™ Expanded Carrier Screen (Quest Diagnostics)	81243, 81443		
	Horizon 27 (27 disease Pan-ethnic Standard Panel) (Natera)	81243, 81257, 81329, 81443		
	Genesys Carrier Panel (Genesys Diagnostics)	0400U		
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 Diagnostics)			
	Foresight Fundamental Panel (Myriad Genetics)			
	Core Carrier Screen (Invitae)			
	UNITY Carrier Screen (BillionToOne)	0449U		
Cystic Fibrosis Carrier Screening				

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
CFTR Targeted Variant Analysis	CFTR Targeted Variants - Single Test (GeneDx)	81221	O09, Z13, Z31, Z36, Z83.49	3
CFTR Sequencing Deletion/Duplication Analysis, or Mutation Panel	Cystic Fibrosis Complete Rare Variant Analysis, Entire Gene Sequence (Quest Diagnostics)	81223		1, 10
	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		1
Spinal Muscular Atrophy Carrier Screening				
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		
Fragile X Syndrome Carrier Screening				
FMR1 Repeat Analysis	Fragile X Syndrome, PCR with Reflex to Southern Blot (Integrated Genetics)	81243, 81244	O09, Z13, Z31, Z34, Z36, Z84	3, 8, 9
	Fragile X Syndrome, PCR and Southern Blot Analysis (Labcorp)			
Hemoglobinopathy Carrier Screening				
HBA1, HBA2, or *HBB* Targeted Variant Analysis	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		

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
HBA1, HBA2, or *HBB* Sequencing and/or Deletion/Duplication Analysis	Alpha-Globin Gene Sequencing and Deletion/Duplication (Quest Diagnostics)	81259, 81269, 81363, 81364		11
	HBA1 Deletion/Duplication (GeneDx) HBA2 Deletion/Duplication (GeneDx)			
	HBB Carrier-Full Gene Sequencing and Deletion/Duplication (Invitae)			
Ashkenazi Jewish Carrier Panel Testing				
Ashkenazi Jewish Carrier Panel Testing	Ashkenazi Jewish Panel (11 Tests) (Quest Diagnostics)	81412	O09, Z13, Z31, Z34, Z36, Z84	3
Duchenne and Becker Muscular Dystrophy Carrier Screening				
DMD Targeted Variant Analysis	DMD Targeted Variants - Single Test (GeneDx)	81479	O09, Z13, Z31, Z34, Z36, Z84	6
DMD Sequencing and/or Deletion/Duplication Analysis	Duchenne/Becker MD (DMD) Gene Sequencing (GeneDx)	81161, 81408		7
	Duchenne/Becker MD (DMD) Del/Dup (GeneDx)			
	Genomic Unity DMD Gene Analysis (Variantyx)	0218U		

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.

back to top

COVERAGE CRITERIA

EXPANDED CARRIER SCREENING PANELS

I. Expanded carrier screening panels (81243, 81257, 81329, 81336, 81405, 81408, 81479, 0400U81443*) 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, 0400U, 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. If 81243 is billed along with 81443, the patient should still meet the specific Fragile X syndrome criteria.

**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.

back to top

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, 0449U) 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, 0449U) 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.

back to top

CYSTIC FIBROSIS CARRIER SCREENING

CFTR Targeted Variant Analysis

I. Cystic fibrosis carrier screening via *CFTR* targeted variant analysis (81221) may be considered **medically necessary** when:

   A. The member 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-100 variant panel, may be considered **medically necessary** when:

   A. The member 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-100 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 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.

back to top

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 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 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).

back to top

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. Additionally, if *FMR repeat analysis* (81243) is billed along with an additional carrier screen panel code (81443), the patient should still meet the above Fragile X syndrome criteria.

back to top

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 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 *HBA1*, *HBA2*, or *HBB.*

II. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81257, 81258), or *HBB* (81361, 81362) targeted variant analysis is considered **investigational** for all other indications.

Note: If a member's reproductive partner is known to be a carrier of a hemoglobinopathy, via genetic testing results and/or hematologic screening results, the more appropriate test for the member is likely *HBA1*, *HBA2*, or *HBB* Sequencing and/or Deletion/Duplication Analysis.

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 or the member's reproductive partner is considering pregnancy or is currently pregnant.

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, including fetal hemoglobin testing via circulating fetal DNA.

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

back to top

ASHKENAZI JEWISH CARRIER PANEL TESTING

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

A. The member 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 Obstetricians and Gynecologists (ACOG):

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. Mucolipidosis IV (*MCOLN1*)
10. Glycogen storage disease type I (*G6PC1*)
11. Joubert syndrome (*TMEM216*)
12. Maple syrup urine disease (*BCKDHB*)
13. Usher syndrome types 1F and III (*PCDH15* and *CLRN1*).

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.

back to top

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.

back to top

PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

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 for autosomal recessive and X-linked conditions. (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 2023), 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 2023), 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 Variant Analysis**

ACOG published practice bulletin No. 691 (March 2017, reaffirmed 2023) 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 2023 position statement for *CFTR* variant testing, the American College of Medical Genetics and Genomics (ACMG) recommends a minimum number of 100 variants tested in the *CFTR* gene if carrier testing is pursued: "The new *CFTR* variant set [n=100; see p. 6] represents an updated minimum recommended variant set for CF [cystic fibrosis] carrier screening, and this new set now supersedes the previous set of 23 *CFTR* variants recommended by the ACMG." (p. 7)

In their 2020 technical standard for *CFTR*, 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, reaffirmed 2023) 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 2023) 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 2023) 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 2023) 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 a Practice Advisory (2022, reaffirmed 2023), which recommends offering universal hemoglobinopathy testing to individuals who are considering pregnancy or who are currently pregnant (at the initial prenatal visit). The testing may be performed using either hemoglobin electrophoresis or molecular testing, such as expanded carrier screening.

Ashkenazi Jewish Carrier Panel Testing

American College of Obstetricians and Gynecologists (ACOG) ACOG published practice bulletin No. 691 (2017, reaffirmed 2023), 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, mucolipidosis 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)

back to top

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back to top

Note: Medica uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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