| BSC_CON_2.07 | Genetic Testing: Prenatal and Preconception Carrier Screening | | |
|---|---|---|---|
| **Original Policy Date:** | February 1, 2023 | **Effective Date:** | May 1, 2024 |
| **Section:** | 2.0 Medicine | **Page:** | Page 1 of 26 |

## Example Test 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

| Policy Statement Sections | Example Tests (Labs) | Common CPT Codes |
|---|---|---|
| Expanded Carrier Screening Panels | Foresight Universal Panel Carrier Screen (Myriad Genetics) | 81329, 81443 |
| | 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 |
| 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 |
| | Inheritest Carrier Screen-Society-Guided Panel (14 Genes) (Labcorp) | |
| | Prenatal Carrier Panel (Quest Diagnostics) | |
| | Foresight Fundamental Panel (Myriad Genetics) | |
| | Core Carrier Screen (Invitae) | |
| **Cystic Fibrosis Carrier Screening** | | |
| *CFTR* Known Familial Variant Analysis | CFTR Targeted Variants - Single Test (GeneDx) | 81221 |
| *CFTR* Sequencing and/or Deletion/Duplication Analysis, or Mutation Panel | Cystic Fibrosis Complete Rare Variant Analysis, Entire Gene Sequence (Quest Diagnostics) | 81223 |
| | 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 |

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| Policy Statement Sections | Example Tests (Labs) | Common CPT Codes |
|---|---|---|
| **Spinal Muscular Atrophy Carrier Screening** | | |
| *SMN1* Targeted Variant Analysis | Spinal Muscular Atrophy - SMN1 Known Variant Testing (Nemours)<br>SMN1 Targeted Variant - 2 Variants Test (GeneDx) | 81337, 81403 |
| *SMN1* Sequencing and/or Deletion/Duplication and *SMN2* Deletion/Duplication Analysis | Spinal Muscular Atrophy Carrier Test (Natera) | 81329, 81336, 81401, 81405 |
| | 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 |
| | 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 |
| | HBA1 Targeted Variant-Single Test (GeneDx)<br>*HBA2* Targeted Variant-Single Test (GeneDx) | |
| | HBB Targeted Variant - Single Test (GeneDx) | 81361, 81362 |
| *HBA1, HBA2,* or *HBB* Sequencing and/or Deletion/Duplication Analysis | Alpha-Globin Gene Sequencing and Deletion/Duplication (Quest Diagnostics) | 81259, 81269, 81363, 81364 |
| | HBA1 Deletion/Duplication (GeneDx)<br>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 |
| **Duchenne and Becker Muscular Dystrophy Carrier Screening** | | |
| *DMD* Targeted Variant Analysis | DMD Targeted Variants - Single Test (GeneDx) | 81479 |
| *DMD* Sequencing and/or Deletion/Duplication Analysis | Duchenne/Becker MD (DMD) Gene Sequencing (GeneDx) | 81161, 81408 |
| | Duchenne/Becker MD (DMD) Del/Dup (GeneDx) | |
| | Genomic Unity DMD Gene Analysis (Variantyx) | 0218U |

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## Policy Statement

### EXPANDED CARRIER SCREENING PANELS

I. Expanded carrier screening panels (81243, 81257, 81329, 81336, 81405, 81408, 81479, 81443*) may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member is considering pregnancy or is currently pregnant**
   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. 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.

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

III. 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 **BOTH** of the following criteria are met:
   A. The member is considering pregnancy or is currently pregnant*
   B. The panel includes the genes *CFTR* and *SMN1*

IV. Basic carrier screening panels (*CFTR, SMN1/2, FMR1, HBB/HBA1/HBA2*, but not more than 14 genes) (81220, 81222, 81223, 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.

### CYSTIC FIBROSIS CARRIER SCREENING

#### *CFTR* Targeted Variant Analysis

V. Cystic fibrosis carrier screening via *CFTR* targeted variant analysis (81221) may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant
   B. The member has a close relative with a known pathogenic or likely pathogenic variant in *CFTR*.

VI. 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

VII. 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 **EITHER** of the following criteria are met:
   A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant

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

VIII. 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)

IX. Analysis of the *CFTR* intron 9 polyT and TG regions (81224) for cystic fibrosis carrier screening may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant
   B. The member is known to have an R117H variant in the *CFTR* gene.

X. 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 Blue Shield of California Medical Policy: *Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay* (to be published) for coverage criteria for genetic testing to establish a diagnosis of cystic fibrosis.

## SPINAL MUSCULAR ATROPHY CARRIER SCREENING

### *SMN1* Targeted Variant Analysis

XI. Spinal muscular atrophy (SMA) carrier screening via *SMN1* targeted variant analysis (81337, 81403) may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant
   B. The member has a close relative with a known pathogenic or likely pathogenic variant in *SMN1*.

XII. 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

XIII. Spinal muscular atrophy (SMA) carrier screening via *SMN1* sequencing and/or deletion/duplication analysis and *SMN2* deletion/duplication analysis (81329, 81336, 81401, 81405, 0236U) may be considered **medically necessary** when **EITHER** of the following criteria are met:
   A. The member or member's reproductive partner is considering pregnancy or is currently pregnant
   B. The member's reproductive partner is a known carrier for spinal muscular atrophy.

XIV. 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 Blue Shield of California Medical Policy: *Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders* (to be published) for coverage criteria for genetic testing to establish a diagnosis of spinal muscular atrophy (SMA).

## FRAGILE X SYNDROME CARRIER SCREENING

### *FMR1* Repeat Analysis

XV. Fragile X carrier screening via *FMR1* CGG-trinucleotide repeat analysis (81243, 81244) may be considered **medically necessary** when **EITHER** of the following criteria are met:

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A. The member has been diagnosed with premature ovarian insufficiency or elevated follicle-stimulating hormone level before age 40 years
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)
      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)
      c. Close relative with unexplained intellectual disability, developmental delay, or autism spectrum disorder
      d. Close relative diagnosed with premature ovarian insufficiency or elevated follicle-stimulating hormone level before age 40 years

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

***NOTE:*** Refer to Blue Shield of California Medical Policy: *Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay* (to be published) for coverage criteria for genetic testing to establish a diagnosis of fragile X syndrome. Additionally, if 81243 is billed along with 81443, the patient should still meet the above Fragile X syndrome criteria.

## HEMOGLOBINOPATHY CARRIER SCREENING

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

XVII. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81257, 81258), or *HBB* (81361, 81362) targeted variant analysis may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant
   B. The member has a close relative with a known pathogenic or likely pathogenic variant in *HBA1*, *HBA2*, or *HBB*

XVIII. 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

XIX. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81259, 81269), or *HBB* (81363, 81364) sequencing and/or deletion/duplication analysis may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant
   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.

XX. 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 Blue Shield of California Medical Policy: *Genetic Testing: Hematologic Conditions (non-cancerous)* (to be published) for coverage criteria for genetic testing to establish a diagnosis of a hemoglobinopathy.

## ASHKENAZI JEWISH CARRIER PANEL TESTING

XXI. Ashkenazi Jewish carrier panel testing (81412) may be considered **medically necessary** when **ALL** of the following criteria are met:

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A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant
B. The member is of Ashkenazi Jewish ancestry
C. The panel includes, at a minimum, screening for carrier status for genetic conditions associated with the following genetic conditions, 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 (*PDCH5* and *CLRN1*)

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

## DUCHENNE AND BECKER MUSCULAR DYSTROPHY CARRIER SCREENING

### *DMD* Targeted Variant Analysis

XXII. Duchenne and Becker muscular dystrophy carrier screening via *DMD* targeted variant analysis (81479) may be considered **medically necessary** when **BOTH** of the following criteria are met:
    A. The member is considering pregnancy or is currently pregnant
    B. The member has a close relative with a known pathogenic or likely pathogenic variant in *DMD*.

XXIII. 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

XXIV. Duchenne and Becker muscular dystrophy carrier screening via *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) may be considered **medically necessary** when **BOTH** of the following criteria are met:
    A. The member is considering pregnancy or is currently pregnant
    B. The member has a first- or second-degree relative diagnosed with Duchenne or Becker muscular dystrophy.

XXV. 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 Blue Shield of California Medical Policy: *Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders* (to be published) for coverage criteria for genetic testing to establish a diagnosis of Duchenne or Becker muscular dystrophy.

**NOTE**: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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## Policy Guidelines

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.

### Coding

See the Codes table for details.

## Description

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

Carrier screening is performed to identify individuals at risk of having offspring with inherited recessive or X-linked single-gene disorders. Carriers are typically asymptomatic but can pass disease-causing variants to their offspring. 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.

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## 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: Non-Invasive Prenatal Screening (NIPS)/ Non-Invasive Prenatal Testing (NIPT)*** 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 ***(to be published)***
- ***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 ***(to be published)***
- ***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.

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

- N/A

## 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

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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.

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## 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,

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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):

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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 2023) 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 (i.e., 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, 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

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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)

## References

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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 2023);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
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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 (Reaffirmed 2021);124(1):193-197. doi:10.1097/01.AOG.0000451757.51964.98
10. Deignan JL, Gregg AR, Grody WW, et al. Updated recommendations for *CFTR* carrier screening: a position statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(8):100867.

## Documentation for Clinical Review

**Please provide the following documentation:**

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:

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- Signs/symptoms leading to a suspicion of genetic condition
- Family history if applicable

- Prior evaluation/treatment:
  - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
  - Family member's genetic test result, if applicable
- Rationale
  - Reason for performing test
  - How test result will impact clinical decision making

**Post Service (in addition to the above, please include the following):**

- Results/reports of tests performed

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

| Type | Code | Description |
|---|---|---|
| CPT® | 0218U | Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants |
| | 0236U | SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (e.g., spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications, deletions, and mobile element insertions |
| | 0400U | Obstetrics (expanded carrier screening), 145 genes by next-generation sequencing, fragment analysis and multiplex ligation-dependent probe amplification, DNA, reported as carrier positive or negative ***(Code effective 7/1/2023)*** |
| | 0449U | Carrier screening for severe inherited conditions (e.g., cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2) ***(Code effective 4/1/2024)*** |
| | 81161 | DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed |
| | 81220 | CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines) |
| | 81221 | CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants |
| | 81222 | CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants |
| | 81223 | CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence |

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| Type | Code | Description |
|---|---|---|
| | 81224 | CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g., male infertility) |
| | 81243 | FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles |
| | 81244 | FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and promoter methylation status) |
| | 81257 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring) |
| | 81258 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant |
| | 81259 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence |
| | 81269 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants |
| | 81329 | SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; dosage/deletion analysis (e.g., carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed |
| | 81336 | SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; full gene sequence |
| | 81337 | SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; known familial sequence variant(s) |
| | 81361 | HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (e.g., HbS, HbC, HbE) |
| | 81362 | HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s) |
| | 81363 | HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s) |
| | 81364 | HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence |
| | 81401 | Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) |
| | 81403 | Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) |
| | 81405 | Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) |
| | 81408 | Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis) |
| | 81412 | Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, |

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| Type | Code | Description |
|---|---|---|
| | | Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1 |
| | 81443 | Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A |
| | 81479 | Unlisted molecular pathology procedure |
| **HCPCS** | None | |

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action |
|---|---|
| 02/01/2023 | New policy. |
| 08/01/2023 | Coding update. |
| 02/01/2024 | Annual review. Policy statement, guidelines and literature updated.<br>Coding update. |
| 05/01/2024 | Coding update. |

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an

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authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

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## Appendix A

| POLICY STATEMENT | |
|---|---|
| **BEFORE**<br>Red font: Verbiage removed | **AFTER**<br>Blue font: Verbiage Changes/Additions |
| **Genetic Testing: Prenatal and Preconception Carrier Screening**<br>**BSC_CON_2.07**<br><br>**Policy Statement:**<br>**EXPANDED CARRIER SCREENING PANELS**<br>I. Expanded carrier screening panels (81443) may be considered **medically necessary** when:<br>A. The member is considering pregnancy or is currently pregnant, AND<br>B. The panel includes CFTR and SMN1.<br><br>II. Expanded carrier screening panels (81443) are considered **investigational** for all other indications. | **Genetic Testing: Prenatal and Preconception Carrier Screening**<br>**BSC_CON_2.07**<br><br>**Policy Statement:**<br>**EXPANDED CARRIER SCREENING PANELS**<br>I. Expanded carrier screening panels (81243, 81257, 81329, 81336, 81405, 81408, 81479, 81443*) may be considered **medically necessary** when **BOTH** of the following criteria are met:<br>A. The member is considering pregnancy or is currently pregnant**<br>B. The panel includes the genes *CFTR* and *SMN1*<br><br>II. Expanded carrier screening panels (81243, 81257, 81329, 81336, 81405, 81408, 81479, 81443*) are considered **investigational** for all other indications.<br><br>*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.<br><br>**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.<br><br>**BASIC CARRIER SCREENING PANELS (Cystic fibrosis, Spinal Muscular Atrophy, Fragile X, Hemoglobinopathies, not more than 14 genes)**<br>III. 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 **BOTH** of the following criteria are met:<br>A. The member is considering pregnancy or is currently pregnant*<br>B. The panel includes the genes *CFTR* and *SMN1* |

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| POLICY STATEMENT | |
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| **BEFORE**<br>Red font: Verbiage removed | **AFTER**<br>Blue font: Verbiage Changes/Additions |
| | IV. Basic carrier screening panels (*CFTR, SMN1/2, FMR1, HBB/HBA1/HBA2*, but not more than 14 genes) (81220, 81222, 81223, 81243, 81257, 81329, 81336) are considered **investigational** for all other indications.<br><br>*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. |
| **CYSTIC FIBROSIS CARRIER SCREENING**<br>***CFTR* Known Familial Variant Analysis**<br>III. Cystic fibrosis carrier screening via *CFTR* targeted mutation analysis (when an expanded carrier panel is not ordered) for a known familial mutation (81221) may be considered **medically necessary** when:<br>A. The member and/or the member's reproductive partner is considering pregnancy or is currently pregnant, **AND**<br>B. The member has a close relative with a known pathogenic or likely pathogenic variant in *CFTR*. | **CYSTIC FIBROSIS CARRIER SCREENING**<br>***CFTR* Targeted Variant Analysis**<br>V. Cystic fibrosis carrier screening via *CFTR* targeted variant analysis (81221) may be considered **medically necessary** when **BOTH** of the following criteria are met:<br>A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant<br>B. The member has a close relative with a known pathogenic or likely pathogenic variant in *CFTR*. |
| IV. Cystic fibrosis carrier screening via *CFTR* targeted mutation analysis for a known familial mutation (81221) is considered **investigational** for all other indications. | VI. 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**<br>V. Cystic fibrosis carrier screening via *CFTR* sequencing (81223, S3835), deletion/duplication analysis (81222) (when an expanded carrier panel is not ordered), may be considered **medically necessary** when:<br>A. The member and/or the member's reproductive partner is considering pregnancy or is currently pregnant, **OR**<br>B. The member's reproductive partner is a known carrier for cystic fibrosis. | ***CFTR* Sequencing, Deletion/Duplication Analysis, or Mutation Panel**<br>VII. 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 **EITHER** of the following criteria are met:<br>A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant<br>B. The member's reproductive partner is a known carrier for cystic fibrosis. |

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| POLICY STATEMENT | |
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| **BEFORE**<br>Red font: Verbiage removed | **AFTER**<br>Blue font: Verbiage Changes/Additions |
| VI. Cystic fibrosis carrier screening via *CFTR* sequencing (81233, S3835), deletion/duplication analysis (81222), or a mutation panel (81220) using at a minimum the ACMG-23 variant panel is considered **investigational** for all other indications. | VIII. 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)** | ***CFTR* Intron 9 PolyT and TG Analysis (previously called Intron 8 polyT/TG Analysis)** |
| VII. Separate or individual analysis of the *CFTR* intron 9 polyT and TG regions (81224) for cystic fibrosis carrier screening may be considered **medically necessary** when:<br>A. The member and/or the member's reproductive partner is considering pregnancy or is currently pregnant, **AND**<br>B. The member is known to have an R117H variant in the *CFTR* gene. | IX. Analysis of the *CFTR* intron 9 polyT and TG regions (81224) for cystic fibrosis carrier screening may be considered **medically necessary** when **BOTH** of the following criteria are met:<br>A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant<br>B. The member is known to have an R117H variant in the *CFTR* gene. |
| VIII. Separate or individual analysis of the *CFTR* intron 9 polyT and TG regions (81224) for cystic fibrosis carrier screening is considered **investigational** for all other indications. | X. Analysis of the *CFTR* intron 9 polyT and TG regions (81224) for cystic fibrosis carrier screening is considered **investigational** for all other indications. |
| **Note**: If fertility benefits allow, testing for male infertility (including *CFTR*) may be medically necessary for congenital bilateral absence of the vas deferens (CBAVD). | |
| Refer to Blue Shield of California Medical Policy: *Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay* (to be published) for coverage criteria for genetic testing to establish a diagnosis of cystic fibrosis (rather than for carrier screening). | ***NOTE:*** Refer to Blue Shield of California Medical Policy: *Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay* (to be published) for coverage criteria for genetic testing to establish a diagnosis of cystic fibrosis. |
| **SPINAL MUSCULAR ATROPHY CARRIER SCREENING**<br>***SMN1* Targeted Variant Analysis** | **SPINAL MUSCULAR ATROPHY CARRIER SCREENING**<br>***SMN1* Targeted Variant Analysis** |
| IX. Separate or individual spinal muscular atrophy (SMA) carrier screening via *SMN1* targeted variant analysis (81337) (when an expanded carrier panel is not ordered) may be considered **medically necessary** when:<br>A. The member and/or the member's reproductive partner is considering pregnancy or is currently pregnant, **AND** | XI. Spinal muscular atrophy (SMA) carrier screening via *SMN1* targeted variant analysis (81337, 81403) may be considered **medically necessary** when **BOTH** of the following criteria are met:<br>A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant |

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| POLICY STATEMENT | |
|---|---|
| **BEFORE**<br>Red font: Verbiage removed | **AFTER**<br>Blue font: Verbiage Changes/Additions |
| B. The member has a close relative with a known pathogenic or likely pathogenic variant in *SMN1*. | B. The member has a close relative with a known pathogenic or likely pathogenic variant in *SMN1*. |
| X. Separate or individual spinal muscular atrophy (SMA) carrier screening via *SMN1* targeted variant analysis (81337) (when an expanded carrier panel is not ordered) is considered **investigational** for all other indications. | XII. Spinal muscular atrophy (SMA) carrier screening via *SMN1* targeted variant analysis (81337, 81403) is considered **investigational** for all other indications. |
| ***SMN1*/*SMN2* Sequencing and/or Deletion/Duplication Analysis** | ***SMN1* Sequencing and/or Deletion/Duplication and *SMN2* Deletion/Duplication Analysis** |
| XI. Separate or individual spinal muscular atrophy (SMA) carrier screening via *SMN1*/*SMN2* sequencing and/or deletion/duplication analysis (81329, 81336) (when an expanded carrier panel is not ordered) is considered **medically necessary** when:<br>A. The member and/or member's reproductive partner is considering pregnancy or is currently pregnant, **OR**<br>B. The member's reproductive partner is a known carrier for spinal muscular atrophy. | XIII. Spinal muscular atrophy (SMA) carrier screening via *SMN1* sequencing and/or deletion/duplication analysis and *SMN2* deletion/duplication analysis (81329, 81336, 81401, 81405, 0236U) may be considered **medically necessary** when **EITHER** of the following criteria are met:<br>A. The member or member's reproductive partner is considering pregnancy or is currently pregnant<br>B. The member's reproductive partner is a known carrier for spinal muscular atrophy. |
| XII. Separate or individual spinal muscular atrophy (SMA) carrier screening via *SMN1*/*SMN2* sequencing and/or deletion/duplication analysis (81329, 81336) (when an expanded carrier panel is not ordered) is considered **investigational** for all other indications. | XIV. 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 Blue Shield of California Medical Policy: *Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders* (to be published) for coverage criteria for genetic testing to establish a diagnosis of spinal muscular atrophy (SMA) (rather than for carrier screening). | ***NOTE:*** Refer to Blue Shield of California Medical Policy: *Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders* (to be published) for coverage criteria for genetic testing to establish a diagnosis of spinal muscular atrophy (SMA). |
| **FRAGILE X SYNDROME CARRIER SCREENING**<br>***FMR1* Repeat Analysis** | **FRAGILE X SYNDROME CARRIER SCREENING**<br>***FMR1* Repeat Analysis** |
| XIII. Fragile X carrier screening via *FMR1* CGG-trinucleotide repeat analysis (81243, 81244) (when an expanded carrier panel is not ordered) may be considered **medically necessary** when: | XV. Fragile X carrier screening via *FMR1* CGG-trinucleotide repeat analysis (81243, 81244) may be considered **medically necessary** when **EITHER** of the following criteria are met: |

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| A. The member has been diagnosed with premature ovarian insufficiency or elevated follicle-stimulating hormone level before age 40 years, OR<br>B. The member is considering a pregnancy or is currently pregnant, **AND**<br>1. The member has one of the following:<br>a) Close relative with Fragile X syndrome (i.e., close relative has >200 CGG repeats in the *FMR1* gene), **OR**<br>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**<br>c) Close relative with unexplained intellectual disability, developmental delay, or autism spectrum disorder, **OR**<br>d) Close relative diagnosed with premature ovarian insufficiency or elevated follicle-stimulating hormone level before age 40 years. | A. The member has been diagnosed with premature ovarian insufficiency or elevated follicle-stimulating hormone level before age 40 years<br>B. The member is considering a pregnancy or is currently pregnant, **AND**<br>1. The member has **one** of the following:<br>a. Close relative with Fragile X syndrome (i.e., close relative has more than 200 CGG repeats in the *FMR1* gene)<br>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)<br>c. Close relative with unexplained intellectual disability, developmental delay, or autism spectrum disorder<br>d. Close relative diagnosed with premature ovarian insufficiency or elevated follicle-stimulating hormone level before age 40 years |
| XIV. Fragile X carrier screening via *FMR1* CGG-trinucleotide repeat analysis (81243, 81244) (when an expanded carrier panel is not ordered) is considered **investigational** for all other indications. | XVI. Fragile X carrier screening via *FMR1* CGG-trinucleotide repeat analysis (81243, 81244) is considered **investigational** for all other indications. |
| **Note**: Refer to Blue Shield of California Medical Policy: *Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay (*to be published) for coverage criteria for genetic testing to establish a diagnosis of fragile X syndrome. | ***NOTE:*** Refer to Blue Shield of California Medical Policy: *Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay (*to be published) for coverage criteria for genetic testing to establish a diagnosis of fragile X syndrome. Additionally, if 81243 is billed along with 81443, the patient should still meet the above Fragile X syndrome criteria. |
| HEMOGLOBINOPATHY CARRIER SCREENING<br>***HBA1*, *HBA2*, or *HBB* Targeted Variant Analysis** | HEMOGLOBINOPATHY CARRIER SCREENING<br>***HBA1*, *HBA2*, or *HBB* Targeted Variant Analysis** |
| XV. Separate or individual hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81257, 81258, S3845, S3846), or *HBB* (81361, 81362) targeted variant analysis (when an expanded carrier panel is not ordered) may be considered **medically necessary** when:<br>A. The member and/or the member's reproductive partner is considering pregnancy or is currently pregnant, **AND**<br>B. The member meets one of the following: | XVII. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81257, 81258), or *HBB* (81361, 81362) targeted variant analysis may be considered **medically necessary** when **BOTH** of the following criteria are met:<br>A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant<br>B. The member has a close relative with a known pathogenic or likely pathogenic variant in *HBA1*, *HBA2*, or *HBB* |

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| 1. The member has a close relative with a known pathogenic or likely pathogenic variant in *HBA1*, *HBA2*, or *HBB*, ***OR***<br>2. The member's reproductive partner is a known carrier of a pathogenic or likely pathogenic variant in *HBA1*, *HBA2*, or *HBB*, **OR**<br>3. The member's reproductive partner is known to have a diagnosis of a hemoglobinopathy, **OR**<br>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. | |
| XVI. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81257, 81258, S3845, S3846), or *HBB* (81361, 81362) targeted variant analysis is considered **investigational** for all other indications. | XVIII. 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**<br>XVII. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81259, 81269, S3845), or *HBB* (81363, 81364, S3846) sequencing and/or deletion/duplication analysis (when an expanded carrier panel is not ordered) may be considered **medically necessary** when:<br>A. The member and/or the member's reproductive partner is considering pregnancy or is currently pregnant, **AND**<br>B. The member meets one of the following:<br>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. | ***HBA1*, *HBA2*, or *HBB* Sequencing and/or Deletion/Duplication Analysis**<br>XIX. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81259, 81269), or *HBB* (81363, 81364) sequencing and/or deletion/duplication analysis may be considered **medically necessary** when **BOTH** of the following criteria are met:<br>A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant<br>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. |
| XVIII. Hemoglobinopathy carrier screening via *HBA1*, *HBA2* (81259, 81269, S3845), or *HBB* (81363, 81364, S3846) sequencing and/or duplication analysis is considered **investigational** for all other indications. | XX. 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 Blue Shield of California Medical Policy: *Genetic Testing: Hematologic Conditions (non-cancerous)* for coverage criteria for genetic testing to establish a diagnosis of a hemoglobinopathy. | ***NOTE:*** Refer to Blue Shield of California Medical Policy: *Genetic Testing: Hematologic Conditions (non-cancerous)* (to be published) for coverage criteria for genetic testing to establish a diagnosis of a hemoglobinopathy. |

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| **ASHKENAZI JEWISH CARRIER PANEL TESTING**<br>XIX. Separate or individual Ashkenazi Jewish carrier panel testing (81412) (when an expanded carrier panel is not ordered) may be considered **medically necessary** when:<br>A. The member and/or the member's reproductive partner is considering pregnancy or is currently pregnant, **AND**<br>B. The member is of Ashkenazi Jewish ancestry, **AND**<br>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):<br>1. Tay Sachs disease (HEXA)<br>2. Canavan disease (ASPA)<br>3. Cystic fibrosis (CFTR)<br>4. Familial dysautonomia (ELP1)<br>5. Bloom syndrome (BLM)<br>6. Fanconi anemia (FANCC)<br>7. Niemann-Pick disease (SMPD1)<br>8. Gaucher disease (GBA)<br>9. Mucolipidosis IV (MCOLN1)<br><br>**Note**: If only one partner is of Ashkenazi Jewish ancestry, then testing of that partner is considered medically necessary. Testing (by carrier panel or single gene testing) of the other partner is considered medically necessary only if the result of testing of the Ashkenazi Jewish partner is positive. In certain circumstances, biochemical or other clinical tests to definitively diagnose carrier status may be appropriate. | **ASHKENAZI JEWISH CARRIER PANEL TESTING**<br>XXI. Ashkenazi Jewish carrier panel testing (81412) may be considered **medically necessary** when **ALL** of the following criteria are met:<br><br>A. The member or the member's reproductive partner is considering pregnancy or is currently pregnant<br>B. The member is of Ashkenazi Jewish ancestry<br>C. The panel includes, at a minimum, screening for carrier status for genetic conditions associated with the following genetic conditions, as recommended by the American College of Obstetricians and Gynecologists (ACOG):<br>1. Tay Sachs disease (*HEXA*)<br>2. Canavan disease (*ASPA*)<br>3. Cystic fibrosis (*CFTR*)<br>4. Familial dysautonomia (*ELP1*)<br>5. Bloom syndrome (*BLM*)<br>6. Fanconi anemia (*FANCC*)<br>7. Niemann-Pick disease type A (*SMPD1*)<br>8. Gaucher disease Type 1 (*GBA*)<br>9. Mucolipidosis IV (*MCOLN1*)<br>10. Glycogen storage disease type I (*G6PC1*)<br>11. Joubert syndrome (*TMEM216*)<br>12. Maple syrup urine disease (*BCKDHB*)<br>13. Usher syndrome types 1F and III (*PDCH5* and *CLRN1*).<br><br>***NOTE:*** If only one partner is of Ashkenazi Jewish ancestry, then testing of that partner may be considered medically necessary. Testing of the other partner may be 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**<br>**DMD Targeted Variant Analysis**<br>XX. Separate or individual Duchenne and Becker muscular dystrophy carrier screening via *DMD* targeted variant analysis (81403) (when an expanded carrier panel is not ordered) may be considered **medically necessary** when:<br>A. The member is considering pregnancy or is currently pregnant, AND<br>B. The member has a close relative with a known pathogenic or likely pathogenic variant in *DMD*.<br><br>XXI. Separate or individual Duchenne and Becker muscular dystrophy carrier screening via *DMD* targeted variant analysis (81403) is considered **investigational** for all other indications.<br><br>***DMD* Sequencing and/or Deletion/Duplication Analysis**<br>XXII. Separate or individual Duchenne and Becker muscular dystrophy carrier screening via *DMD* sequencing and/or deletion/duplication analysis (81161, 81408) (when an expanded carrier panel is not ordered) may be considered **medically necessary** when:<br>A. The member is considering pregnancy or is currently pregnant, AND<br>B. The member has one of the following:<br>1. First- or second-degree male relative diagnosed with Duchenne or Becker muscular dystrophy.<br><br>XXIII. Separate or individual Duchenne and Becker muscular dystrophy carrier screening via *DMD* sequencing and/or deletion/duplication analysis (81161, 81408) is considered **investigational** for all other indications.<br><br>Note: Refer to Blue Shield of California Medical Policy: *Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders* (to be published) for coverage criteria for genetic testing to establish a diagnosis of Duchenne or Becker muscular dystrophy. | **DUCHENNE AND BECKER MUSCULAR DYSTROPHY CARRIER SCREENING**<br>***DMD* Targeted Variant Analysis**<br>XXII. Duchenne and Becker muscular dystrophy carrier screening via *DMD* targeted variant analysis (81479) may be considered **medically necessary** when **BOTH** of the following criteria are met:<br>A. The member is considering pregnancy or is currently pregnant<br>B. The member has a close relative with a known pathogenic or likely pathogenic variant in *DMD*.<br><br>XXIII. Duchenne and Becker muscular dystrophy carrier screening via *DMD* targeted variant analysis (81479) is considered **investigational** for all other indications.<br><br>***DMD* Sequencing and/or Deletion/Duplication Analysis**<br>XXIV. Duchenne and Becker muscular dystrophy carrier screening via *DMD* sequencing and/or deletion/duplication analysis (81161, 81408, 0218U) may be considered **medically necessary** when **BOTH** of the following criteria are met:<br>A. The member is considering pregnancy or is currently pregnant<br>B. The member has a first- or second-degree relative diagnosed with Duchenne or Becker muscular dystrophy.<br><br>XXV. 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.<br><br>***NOTE:*** Refer to Blue Shield of California Medical Policy: *Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders* (to be published) 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**<br>**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.<br><br>Targeted carrier screening is defined as a test that screens for a known mutation in one gene associated with a specific genetic condition.<br><br>XXIV. 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:<br>A. The member is considering pregnancy or is currently pregnant, **AND**<br>B. The genetic disorder is an autosomal recessive or X-linked condition, **AND**<br>C. One of the following:<br>1. The member has a close relative with a known pathogenic or likely pathogenic variant associated with the disorder, **OR**<br>2. The member's reproductive partner is a carrier for the genetic disorder, **OR**<br>3. The member or the member's reproductive partner has a first- or second-degree relative who is affected with the genetic disorder.<br><br>XXV. 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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