# Corporate Medical Policy

# Genetic Testing for FMR1 Mutations AHS – M2028

**File Name:** genetic_testing_for_fmr1_mutations
**Origination:** 01/01/2019
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## Description of Procedure or Service

**Description**

Fragile X syndrome (FXS) is an X-linked disorder resulting from a loss of function mutation of the Fragile X Mental Retardation-1 (*FMR1*) gene (Saul & Tarleton, 1993); FXS is the most common cause of heritable intellectual disability (Coffee et al., 2009). *FMR1*-related disorders include FXS, fragile X-associated tremor/ataxia syndrome (FXTAS), and *FMR1*-related primary ovarian insufficiency (FRPOI). FXS results in a range of physical, cognitive, and behavioral effects of variable severity (Mila et al., 2016), generally characterized by moderate intellectual disability and autistic characteristics in affected males and mild intellectual disability and emotional and/or psychiatric problems in affected females (Mila et al., 2016; Monaghan et al., 2013).

For guidance on prenatal or preconception screening for FXS, please see Prenatal Screening (Genetic) AHS-M2179.

**Related Policies**

General Genetic Testing, Germline Disorders AHS-M2145

General Genetic Testing, Somatic Disorders AHS-M2146

Genetic Testing for Neurodegenerative Disorders AHS-M2167

Testing for Autism Spectrum Disorder and Developmental Delay AHS-M2176

Prenatal Screening (Genetic) AHS-M2179

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## Policy

**BCBSNC will provide coverage for genetic testing for FMR1 mutations when it is determined the medical criteria guidelines below are met.**

## Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Genetic Testing for FMR1 Mutations is covered

1. For individuals who have received genetic counseling, diagnostic genetic testing for *FMR1* gene CGG repeats (including AGG interruption testing) and methylation status is considered medically necessary for **any** of the following conditions:
   A. For individuals with unexplained mental retardation, developmental delay, or autism spectrum disorder.
   B. For symptomatic individuals with features of Fragile X syndrome or a family history of Fragile X syndrome.
   C. For females with unexplained ovarian insufficiency, unexplained ovarian failure, or unexplained elevated FSH prior to 40 years of age.
   D. For individuals with unexplained late-onset tremor-ataxia.
   E. For fetuses and offspring of known *FMR1* premutation or full mutation carriers.

## When Genetic Testing for FMR1 Mutations is not covered

Genetic screening for *FMR1* gene CGG repeat length more than once per lifetime is considered not medically necessary.

Determination of *FMR1* gene point mutations is considered not medically necessary.

Determination of *FMR1* gene deletion is considered not medically necessary.

General population screening for Fragile X syndrome is considered not medically necessary.

Cytogenetic testing for Fragile X syndrome is considered not medically necessary.

Testing for the FMRP protein is considered not medically necessary.

## Policy Guidelines

**Scientific Background**

Fragile X Syndrome (FXS) and related disorders affects about one in 4,000 males and one in 6,000 to 8,000 females in America (NORD, 2017). Transmitted as an X-linked dominant trait with reduced penetrance, FXS is associated with a fragile site on the X chromosome (Yu et al., 1991) identified as the *Fragile X Mental Retardation-1* (*FMR1*) gene (Santoro et al., 2012). More than 99% of patients with FXS have a mutation in this gene with over 200 CGG repeats and atypical methylation (NORD, 2017). The protein encoded by *FMR1* (FMRP) is a multifunctional RNA-binding protein that regulates the translation of a subset of dendritic mRNAs and plays a central role in neuronal development and synaptic plasticity (Antar et al., 2006; Ascano et al., 2012; Bechara et al., 2009; Castagnola et al., 2018; Didiot et al., 2008; Kenny et al., 2014; Parvin et al., 2018; Yang et al., 2018).

The absence of FMRP results in excessive and persistent mGluR-mediated protein synthesis in postsynaptic dendrites, dysregulation of ion homeostasis, and disruption of calcium ion homeostasis leading to abnormal synaptic signaling and dendritic development (Bear et al., 2004; Castagnola et al., 2018; Finucane et al., 2012). The typical clinical phenotype includes intellectual disability, social impairment, autism spectrum disorder, speech and language delay, neurological dysfunction (seizures and abnormal sleep patterns), sensory hypersensitivity (Rais et al., 2018), and a characteristic physical appearance that typically develops in the second decade of life (Hersh & Saul, 2011). Autism disorders are seen in approximately one third of FXS patients, affecting males more frequently than females (Ormazabal et al., 2019). Between 55 and 90% of patients with autism and FXS report gaze

aversion, hand flapping, repetitive behaviors, reduced social interaction, anxiety, speech preservations, and aggressive behaviors (Reisinger et al., 2020).

Any genetic alteration that results in a lack of functional FMRP can cause FXS symptoms. The most common type of mutation of *FMR1* is the expansion of a CGG trinucleotide repeat in the 5′ untranslated region of the gene (Jin & Warren, 2000). Normally, this ranges in size from seven to about 60 repeats, with 30 being most common (Peprah, 2012). The full mutation consists of expansions of over 200 repeats which become abnormally hypermethylated, silencing the *FMR1* gene and expression of FMRP (Maurin et al., 2014; Oberle et al., 1991). Molecular clinical correlations have shown that the resulting phenotype is related to the degree of methylation and mosaicism rather than the number of repeats (Hersh & Saul, 2011).

Alleles with 55 to 200 CGG repeats are generally unmethylated with normal transcript and FMRP level; however, they are extremely unstable during transmission to the next generation and are referred to as premutations (Zafarullah et al., 2020). Although premutation carriers produce normal levels of FMRP, mRNA levels are elevated, causing toxic effects such as protein sequestration and mitochondrial dysfunction (Garcia-Arocena & Hagerman, 2010; Tassone et al., 2000). As a consequence, RNA toxicity leads to neuronal toxicity and a spectrum of pre-mutation associated disorders such as primary ovarian insufficiency (FXPOI) (Rosario & Anderson, 2020) and tremor ataxia syndrome (FXTAS) (Zafarullah et al., 2020). An increased frequency of neurological, psychological, endocrine, and immune-related characteristics has been documented in premutation carriers (Hagerman & Hagerman, 2013; Raspa et al., 2018). Those with the premutation have higher rates of anxiety, depression, autistic traits, and physical health symptoms such as chronic fatigue and pain, fibromyalgia, and sleep disorders (Johnson et al., 2020).

It has been found that AGG interruptions (when an error in DNA replication results in an AGG interrupting the CGG repeat tract with *FMR1*) may affect the stability of the fragile X triplet repeat in a positive manner. The presence of an AGG interruption has been found to substantially impact the risk of a full-mutation expansion from a given repeat length. There is an emerging role for AGG genotyping to "clarify the course of fragile X genetic diagnosis, counseling, and patient management" (Latham et al., 2014). Others have also noted that the risk of unstable transmissions should be based on the presence or absence of AGG interruptions, not on the classical cutoffs which define the risk categories of *FMR1* alleles (Villate et al., 2020).

***Analytical Validity***

While many fragile X testing methods have been developed, no single approach can characterize all aspects of *FMR1* mutations and expansions, especially when mosaicism is taken into consideration (Monaghan et al., 2013). In a diagnostic setting, it is important to not only detect presence of the CGG expansion, but to also determine its size and methylation status (Lim et al., 2017). Molecular diagnostic testing of *FMR1* currently relies on a combination of polymerase chain reaction (PCR) and Southern blot (the gold standard) for the CGG-repeat expansion and methylation analyses (Cai et al., 2019; Rajan-Babu & Chong, 2016). Detection of rare point mutations and deletions requires sequence analysis (Sitzmann et al., 2018; Suhl & Warren, 2015). This has limited the ability to implement any type of population screening (Riley & Wheeler, 2017).

CGG repeat-primed PCR designed to detect the full range of fragile X expanded alleles followed by analysis via capillary electrophoresis (Chen et al., 2010; Lyon et al., 2010) and melt curve techniques (Rajan-Babu et al., 2015; Teo et al., 2012) minimizes the need for Southern blot analysis. The FastFraX *FMR1* test was evaluated in 198 archived clinical samples, yielding results of 100% sensitivity (95% CI, 91.03% to 100%) and 100% specificity (95% CI, 97.64% to 100%) in categorizing patient samples into the respective normal, intermediate, premutation, and full mutation genotypes (Lim et al., 2017).

The triplet-primed PCR method (dTP-PCR) has been validated by comparison to Southern blot analysis for use in determining mutations in the *FMR1* gene; clinical performance was confirmed with 40 samples resulting in 100% sensitivity and 90.48% specificity in the detection of CGG repeats



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greater than 30 (Skrlec et al., 2018). This testing method may be utilized to screen a general population by quickly determining specific allelic changes in the *FMR1* gene (Skrlec et al., 2018).

Immunohistochemical detection of FMRP has been validated in lymphocytes and chorionic villi samples as an alternative prenatal diagnostic method for detection of full mutations in male fetuses; however, staining is more complex in female fetuses due to X-inactivation and is insufficient for diagnostic use (Oostra & Willemsen, 2001; Willemsen et al., 2002). Clinical and analytical specificity and sensitivity of cytogenetic analysis for FXS are both insufficient (Monaghan et al., 2013).

In a retrospective design, Ramos et al. (2020) studied the performance of the commercial FragileEase PCR kit for FXS diagnosis and compared it to Southern blotting (SB), PCR, and AmplideX FMR1 PCR. Ninety DNA samples were analyzed using FragileEase from patients with a clinical suspicion of FXS or a family history and was compare with the results from the other methods. Overall, FragileEase PCR kit had high concordance with the results from PCR, SB, and AmplideX. FragileEase was able to detect normal, intermediate/gray zone, premutation, and full mutation alleles along with female homozygosity and mosaicism. The authors conclude that "FragileEase™ PCR, as well as other commercially available kits, efficiently detect *FMR1* mutations and simplify the workflow in laboratories that performing FXS diagnoses" (Ramos et al., 2020).

***Clinical Utility and Validity***

As the clinical phenotype of FMR-related diseases can be subtle, its detection, especially in the prepubertal period, can be difficult. Although phenotypic symptoms are not obvious at birth, both animal and neuroimaging studies suggest that the effects of FXS begin in the prenatal period (Riley & Wheeler, 2017). Families report significant delays in diagnosis of FXS with 24% of families reporting that they had seen a healthcare provider more than 10 times before testing. On average, caregivers or other individuals first report concern in regard to the child's development by 13 months; however, professional confirmation of a developmental delay did not occur until an average age of 21 months, and the FXS diagnosis did not occur until an average age of nearly 32 months. Meanwhile, many families had additional children with FXS before becoming aware of the reproductive risk (Bailey et al., 2003). Establishing a diagnosis of FXS allows for an understanding of the disorder and education on appropriate management strategies. Psychopharmacologic intervention to modify behavioral problems, such as attentional deficits, impulse control, anxiety, and emotional lability in a child with FXS can be important in addition to speech therapy, occupational therapy, special educational services, and behavioral interventions (Hersh & Saul, 2011). A recent pilot of allopregnanolone in six males with FXTAS showed significant improvement in GABA metabolism, oxidative stress, and some of the mitochondria-related outcomes (Napoli et al., 2018).

Huang et al. (2019) utilized a GC-rich PCR method to detect *FMR1* gene mutations in 30 pregnant woman who were known carriers of *FMR1* mutations or who contained *FMR1* gene deletion mosaicism; samples utilized chorionic villus, amniotic fluid, or umbilical blood samples. Southern blotting was used as a confirmatory measure. PCR results showed that 18 fetuses were normal, while others presented with full *FMR1* gene mutations, premutations, and/or mosaicism. Even with successful results, the authors state that the use of a single detention method may not be sufficient in determining *FMR1* genetic mutations (Huang et al., 2019).

Lee et al. (2020) utilized a customized PCR and software system to detect the *FMR1* gene expansions from dried blood spots (DBS) and performed analytical validity studies to determine its accuracy, specificity, sensitivity, and precision to be used for newborn screening. The study investigated 963 newborn dried blood spots, which were studied by DNA extraction, *FMR1* PCR amplification, and capillary electrophoresis for automated CGG repeat analysis. While previous *FMR1* newborn screening assays were unsuitable for a routine laboratory setting, this fit-for-purpose *FMR1* screening method provides a reliable method for newborn screening that is both cost-effective and compatible with simple DBS elution methods already used in newborn screening laboratories. From the 963 DBS samples tested, 957 samples (99.4%) samples were classified as normal and six samples (0.6%) had premutation alleles with 55-76 CGG repeat expansions. Five out of the six premutation samples had one normal allele in addition to the premutation allele, while one out of the six had only one allele. Accuracy testing results were 100% concordance with reference genotypes with no false positive or false negative test results found. CGG expansions were consistently within six CGG repeats for larger



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expansions up to 200, within three CGG repeats for expansions up to 137, and within a single repeat for CGG expansions less than 80. However, the authors wrote that "further studies are required to identify if early screening of Fragile X syndrome would lead to better outcomes for the children, families, and society" (Lee et al., 2020).

Approximately twenty individuals have been reported with rare missense or nonsense mutations in the *FMR1* gene; also reported were other coding disturbances of the same gene resulting in physical, cognitive, and behavioral features similarly seen in FXS (Sitzmann et al., 2018). Studies of other FMR mutations that can affect the level and function of the protein include analysis of SNPs showing that 31.66 % of the *FMR1* gene SNPs were disease-related and that 50% of SNPs from online databases had a pathogenic effect (Tekcan, 2016). Screening of 508 males with clinical signs of mental retardation and developmental delay, but without CGG and GCC repeat expansions in the *FMR1* gene, revealed two missense mutations in the *FMR1* gene that would have not been diagnosed with standard molecular testing for FXS (Handt et al., 2014).

Cao et al. (2021) studied the clinical utility of screening *FMR1* gene mutations during early and middle pregnancy for those carrying high-risk CGG trinucleotide expansions. DNA samples from,316 pregnant women at 12-21 gestational weeks were collected and analyzed for CGG repeats using fluorescence PCR and capillary electrophoresis. The carrier rate of CGG repeats was one in 178 for the intermediate type and one in 772 for the premutation types. The highest frequency allele of CGG was 29 repeats, which accounted for 49.29%, followed by 30 repeats (28.56%) and 36 repeats (8.83%). In one case of a premutation type of CGG expansion, the couple chose to terminate the pregnancy. The authors conclude that "pregnant women should be screened for *FMR1* gene mutations during early and middle pregnancy, and those with high-risk CGG expansions should undergo prenatal diagnosis, genetic counseling and family study" (Cao et al., 2021). Ramos et al. (2021) conducted a cross-sectional study on *FMR1* gene mutations in 52 Brazilian women diagnosed with primary ovarian insufficiency. The authors extracted genomic DNA and used FragileEase PCR kits to analyze CGG trinucleotide repeat expansions in the *FMR1* gene. In total, 3.8% of participants had *FMR1* mutations. The authors further concluded that "the most frequent CGG-repeat sizes were 28 and 30" (Ramos et al., 2021).

Fisher et al. (2021) studied the predisposition of carriers to a neurodegenerative disease called Fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is caused by "expansions of the CGG repeats in the 5' upstream region of the FMR1 gene from the normal range" (Fisher et al., 2021) The authors noted that individuals in the premutation group showed CGG expansion sizes with a peak in the 80-99 repeat size range. The two groups in the study included 33 participants who were controls and 41 participants who were FMR1 premutation carriers. The authors were interested in the role of mitochondrial dysfunction and associated cellular-stress signaling in carriers versus healthy control subjects. Results confirmed "the elevation of AMPK and mitochondrial respiratory activities and reduction in reactive $O_2$ species (ROS) levels in premutation cells and revealed for the first time that target of rapamycin complex I (TORC1) activities are reduced" (Fisher et al., 2021). This study also confirmed findings of a previous study in which they reported significant elevation of mitochondrial respiratory functions in FMR1 premutation carriers.

Lindstrand et al. (2022) conducted a study comparing diagnostic methods in patients with intellectual disability and neurodevelopmental disorders using genome sequencing or chromosomal microarray with or without *FMR1* analysis. From the genomic sequencing tests, when using it first, the diagnostic yield was 35%, 26% for when genomic sequencing was second, and 11% for CMA with or without FMR1 analysis. They also identified that costs were higher with CMA/FMR1, and that the majority (91%) of those with a negative result from the CMA/FMR1 analysis remain undiagnosed of definitive intellectual disability or neurodevelopmental disorder. This demonstrated that genome testing may be superior to traditional CMA and FMR1 analysis as a first-line test for those with neurocognitive difficulties, thus rendering it a faster and more cost effective method that is worth further investigating (Lindstrand et al., 2022).



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**Guidelines and Recommendations**

**American College of Medical Genetics and Genomics (ACMG)**

The American College of Medical Genetics and Genomics (ACMG) recommends FXS molecular genetic testing for:

"Fragile X syndrome:

- Individuals of either sex with mental retardation, developmental delay, or autism, especially if they have (a) any physical or behavioral characteristics of fragile X syndrome, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation.
- Individuals seeking reproductive counseling who have (a) a family history of fragile X syndrome or (b) a family history of undiagnosed mental retardation.
- Fetuses of known carrier mothers.
- Affected individuals or their relatives in the context of a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. The cytogenetic test was used prior to the identification of the FMR1 gene and is significantly less accurate than the current DNA test. DNA testing on such individuals is warranted to accurately identify premutation carriers and to distinguish premutation from full mutation carrier women.

Ovarian dysfunction:

- 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.

Tremor/ataxia syndrome:

- Men and women who are experiencing late onset intention tremor and cerebellar ataxia of unknown origin, especially if they have (a) a family history of movement disorders, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation" (Sherman et al., 2005).



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The 2013 ACMG Fragile X testing standards and guidelines, with the American Congress of Obstetricians and Gynecologists, published the following indications for fragile X diagnostic testing and carrier detection:

- "The identification of a full mutation in a male is considered diagnostic rather than predictive, inasmuch as penetrance of fragile X syndrome is virtually 100% in males and the age of onset is not variable
- The identification of a full mutation in a female may be diagnostic, but [over] 50% of females with full mutations have intellectual disability. They may, however, have some manifestations of the disease such as avoidance personality, mood, or stereotypic disorders. Nonrandom X inactivation may explain the milder phenotype in females, although the extent of symptoms cannot be determined by X-inactivation patterns from diagnostic tests that determine the expansion and methylation in blood.
- The identification of a premutation in an asymptomatic male or female undergoing carrier testing (e.g., due to a family history of intellectual disability) is predictive because FXPOI and FXTAS are not fully penetrant and are dependent on both age and allele size.
- All positive results should state that genetic counseling is recommended and testing is available for at-risk family members" (Monaghan et al., 2013).

In 2021, ACMG released an updated guideline for screening for autosomal recessive and X-linked conditions during pregnancy and preconception. Their practice resource aims to recommend "a consistent and equitable approach for offering carrier screening to all individuals during pregnancy and preconception" and replaces any earlier ACMG position statements on prenatal/preconception expanded carrier screening and provide the following recommendations:

- "Carrier screening enables those screened to consider their reproductive risks, reproductive options, and to make informed decisions."
- "The phrase "expanded carrier screening" be replaced by "carrier screening"."
- "Adopting a more precise tiered system based on carrier frequency:
    - Tier 4: <1/200 carrier frequency (includes Tier 3) genes/condition will vary by lab
    - Tier 3: ≥ 1/200 carrier frequency (includes Tier 2) includes X-linked conditions
    - Tier 2: ≥1/100 carrier frequency (includes Tier 1)
    - Tier 1: *CF* [Cystic Fibrosis] + *SMA* [spinal muscular atrophy] + Risk Based Screening
        - "Tier 1 screening conveys the recommendations previously adopted by ACMG and ACOG" and "adopts an ethnic and population neutral approach when screening for cystic fibrosis and spinal muscular atrophy. Beyond these two conditions, additional carrier screening is determined after risk assessment, which incorporates personal medical and family history as well as laboratory and imaging information where appropriate"
        - "Tier 2 carrier screening stems from an ACOG recommendation for conditions that have a severe or moderate phenotype and a carrier frequency of at least 1/100." However, "data demonstrate that carrier screening for two common conditions using a carrier frequency threshold of 1/100 may not be equitable across diverse populations. Others have shown that limiting the carrier frequency to ≥1/100 creates missed opportunities to identify couples at risk for serious conditions."
        - "We define Tier 3 screening as carrier screening for conditions with a carrier frequency ≥1/200 . . . Tier 2 and Tier 3 screening prioritize carrier frequency as a way to think about conditions most appropriate for screening in the general population. However, when ACOG proposed this level, they did not specify whether it was thinking about carrier frequency in terms of the global population or subpopulations. We use "carrier frequency" to mean in any ethnic group with reasonable representation in the United States."
        - "Tier 4 includes genes less common than those in Tier 3 and can identify additional at-risk couples. Tier 4 has no lower limit carrier screening frequency and can greatly extend the number of conditions screened . . . the clinical validity at this level of carrier screening may be less compelling, therefore we suggest reserving this level of screening for consanguineous pregnancies (second cousins or closer) and in couples where family or medical history suggests Tier 4 screening might be beneficial . . . Importantly, patients should understand that their chance of being a carrier for one or more conditions increases as the number of conditions screened is increased."



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- "All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening.
- Tier 4 screening should be considered:
  - When a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer);
  - When a family or personal medical history warrants.
- ACMG does NOT recommend:
  - Offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups.
  - Routine offering of Tier 4 panels.
- "Carrier screening paradigms should be ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion."
- "All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening for … X-linked (Table 6) conditions."
- "All XX patients should be offered screening for only those X-linked genes listed in Table 6 as part of Tier 3 screening."
- "When Tier 1 or Tier 2 carrier screening was performed in a prior pregnancy, Tier 3 screening should be offered" (Gregg et al., 2021).

**Table 6.** X-linked genes recommended for carrier screening.

| OMIM gene | OMIM gene name | OMIM phenotype | Phenotype |
|---|---|---|---|
| 300371 | *ABCD1* | 300100 | Adrenoleukodystrophy (ALD) |
| 300806 | *AFF2* | 309548 | Mental retardation, X-linked, associated with fragile site FRAXE |
| 300382 | *ARX* | 308350 | Developmental and epileptic encephalopathy 1 (DEE1) |
| 300377 | *DMD* | 300376 | Muscular dystrophy, Becker type (BMD) |
| | | 310200 | Muscular dystrophy, Duchenne type (DMD) |
| 306700 | *F8* | 300841 | Hemophilia A (HEMA) |
| 300746 | *F9* | 306900 | Hemophilia B (HEMB) |
| 309550 | *FMR1* | 300624 | Fragile X syndrome (FXS) |
| 300644 | *GLA* | 301500 | Fabry disease |
| 308840 | *L1CAM* | 307000 | Hydrocephalus due to congenital stenosis of aqueduct of Sylvius (HSAS) |
| 300552 | *MID1* | 300000 | Opitz GBBB syndrome, type I (GBBB1) |
| 300473 | *NR0B1* | 300200 | Adrenal hypoplasia, congenital (AHC) |
| 300461 | *OTC* | 311250 | Ornithine transcarbamylase deficiency |
| 300401 | *PLP1* | 312920 | Spastic paraplegia 2, X-linked (SPG2) |
| 312610 | *RPGR* | 300029 | Retinitis pigmentosa 3 (RP3; RP) |
| | | 300455 | Retinitis pigmentosa, X-linked, and sinorespiratory |
| | | 300834 | Infections, with or without deafness |
| | | | Macular degeneration, X-linked atrophic |
| 300839 | *RS1* | 312700 | Retinoschisis 1, X-linked, juvenile (RS1) |
| 300036 | *SLC6A8* | 300352 | Cerebral creatine deficiency syndrome 1 (CCDS1) |

*OMIM* Online Mendelian Inheritance in Man.[55]

Table six from (Gregg et al., 2021)



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**The American College of Obstetricians and Gynecologists (ACOG)**

The American College of Obstetricians and Gynecologists (ACOG) published committee opinion 691 (ACOG, 2017) which recommends Fragile X premutation carrier screening 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 FXS should be offered to known carriers of the fragile X premutation or full mutation (ACOG, 2017).

This guideline was reaffirmed in 2023 (ACOG, 2017).

**Society of Obstetricians and Gynecologists of Canada (SOGC) and Canadian College of Medical Geneticists (CCMG) Guidelines**

Guidelines for FXS genetic testing were given in a joint statement from the SOGC and CCMG. It is stated that "Any woman with a personal or family history of Fragile X- or Fragile X mental retardation 1–related disorders; unexplained intellectual disability or developmental delay; autism; ovarian insufficiency with elevated follicle stimulating hormone at age < 40 years of unknown etiology; or any woman with a family history of male relatives with developmental delay, autism, or isolated cerebellar ataxia and tremor should be offered screening for this condition (II-2A) (GRADE moderate/moderate)" (Wilson et al., 2016). It is also stated that "Population carrier screening for Fragile X syndrome in all women of reproductive age cannot be recommended at this time (II-2D) (GRADE moderate/moderate)" and "Fragile X carrier testing must only occur after detailed genetic counselling and informed consent from the woman to be tested has been obtained (III-A) (GRADE low/moderate)" (Wilson et al., 2016). This statement has since been retired as of 2023. The most updated guidelines regarding prenatal screening for fetal aneuploidy, fetal anomalies, and adverse pregnancy outcomes as well as guidelines for using chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss from SOGC and CCMG do not make a direct mention of FXS genetic testing (Armour et al., 2018; Audibert et al., 2017)e.

**National Society of Genetic Counselors (NSGC)**

The National Society of Genetic Counselors published guidelines, which recommend: "Centers offering population screening should ensure that they have the resources available to provide pre- and post-test genetic counseling that supports the psychosocial and clinical needs of the patient and family. In light of widespread *FMR1* testing among women without known risk factors, genetic counselors should anticipate seeing patients who did not receive any pre-test information, have no prior knowledge of *FMR1*-associated disorders, and are unprepared to learn that they have an *FMR1* mutation. Prenatal diagnosis should be offered to women with pre- or full mutations. Males with premutation alleles should receive genetic counseling about potential phenotypic risks to their daughters, all of whom will inherit premutations" (Finucane et al., 2012).

**American Academy of Pediatrics Committee on Genetics (AAP)**

The American Academy of Pediatrics recommends testing for FXS in children with any of the following, particularly when associated with physical and behavioral characteristics of FXS or a relative with undiagnosed intellectual disability: developmental delay, borderline intellectual abilities or intellectual disability, or diagnosis of autism without a specific etiology (Hersh & Saul, 2011).

**European Molecular Genetics Quality Network (EMQN)**

The EMQN published their best practice guidelines concerning FXS and fragile X-associated disorders in 2015. They state, "Prenatal testing is not indicated for the pregnant partner of a male with a premutation." but they do recommend offering prenatal diagnosis to any woman with 55 or more CGG repeats; "Prenatal testing may be considered for a female fetus of a full mutation father as a cautionary measure (full mutation or MoMP [mosaic premutation and full mutation] or MoMe [methylation mosaic])." Concerning molecular diagnostic analysis in FXS and fragile X-associated disorders, they state the following:

"It is best practice to use a method which detects the whole range of expansions when testing relatives (including prenatal diagnosis) in a family with any known fragile X disorder due to expansion. When testing the *FMR1* gene in population screening, the report must specify that rare cases of point mutation or deletion cannot be detected, nor rare cases of CGG expansion mosaicism (MoMN) if the method used cannot detect the whole range of expansions. It could be useful to confirm results by an independent method when detecting an expansion in an index case depending on specific pitfalls of each method" (Biancalana et al., 2015).

**State and Federal Regulations, as applicable**

**Food and Drug Administration (FDA)**

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

## Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81243, 81244, 88248, 96040, S0265*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 3/2020

Medical Director review 3/2020

Specialty Matched Consultant Advisory Panel review 3/2021

Medical Director review 3/2021

Medical Director review 1/2022

Medical Director review 7/2022

Medical Director review 1/2023

Medical Director review 1/2024

## Policy Implementation/Update Information

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|---|---|
| 1/1/2019 | BCBSNC will provide coverage for genetic testing for FMR1 mutations when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. (jd) |
| 4/1/2019 | Description, background and federal application sections updated. Policy guidelines and references updated. Added 81171 and 81172 to Billing/Coding section as these two codes were accidentally omitted from the 1/1/19 implementation. Medical Director review 4/2019. (jd) |
| 10/29/19 | Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medically Necessity to Reimbursement language, where needed. (hb) |
| 2/11/20 | Annual review by Avalon 4th Quarter 2019 CAB. Billing/Coding section: removed the following codes from the policy – 81171, 81172, 81470, 81472 and added 88248. No change to policy intent. Medical Director review 12/2019. (jd) |
| 3/31/20 | Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director review 3/2020. (jd) |
| 2/9/21 | Annual review by Avalon 4th Quarter 2020 CAB. Related Policy section added. Minor updates to policy guidelines. No change to policy intent. Medical Director review 1/2021. (jd) |
| 3/31/21 | Specialty Matched Consultant Advisory Panel review 3/2021. Medical Director review 3/2021. (jd) |
| 2/8/22 | Reviewed by Avalon 4th Quarter 2021 CAB. Description, policy guidelines, and references updated with minor revisions. Medical Director review 1/2022. (jd) |

9/13/22 Off-cycle review by Avalon 2nd Quarter 2022 CAB. Description, policy guidelines, and references updated. Billing/Coding section updated. The following updates made to the When Covered section: 2e updated and now reads "Fetuses and offspring of known FMR1 premutation or full mutation carriers", 3 edited to remove family history requirements. removed all subcriteria. Not Covered section updated to include statement: "Genetic screening for FMR1 gene CGG repeat length more than once per lifetime is considered not medically necessary." Medical Director review 7/2022. (tm)

2/7/23 Reviewed by Avalon 4th Quarter 2022 CAB. Related policies section removed, When Covered section edited to combine previous coverage criteria 1 and 2 and now reads "Reimbursement is allowed for individuals who have received genetic counseling, diagnostic genetic testing for FMR1 gene CGG repeats and methylation status for any of the following conditions:". Not Covered section edited for clarity, Policy guidelines, and References updated. No change to policy statement. Medical Director review 1/2023. (tm)

10/24/23 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Reimbursement to Medical Necessity. (tm)

2/21/24 Reviewed by Avalon 4th Quarter 2023 CAB. Related Policies added to Description section. The following statement was added to the Description section "For guidance on prenatal or preconception screening for FXS, please see Prenatal Screening (Genetic) AHS-M2179." When Covered section updated as follows: coverage criteria 1 now reads: "For individuals who have received genetic counseling, diagnostic genetic testing for *FMR1* gene CGG repeats (including AGG interruption testing) and methylation status is considered medically necessary for **any** of the following conditions", removed previous coverage criteria 2 "For individuals seeking pre-conception or prenatal care, carrier screening for *FMR1* gene CGG repeat length is considered medically necessary". Policy Guidelines and References updated. Medical Director review 1/2024. (tm)

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