

<b>2.04.83 Genetic Testing for FMR1 Variants (Including Fragile X Syndrome)</b>			
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<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 15

## Policy Statement

- I. Genetic testing for fragile X mental retardation 1 gene (*FMR1*) variants may be considered **medically necessary** for **any** of the following populations:
  - A. Individuals with characteristics of fragile X syndrome (FXS) or a fragile X-associated disorder, including:
    1. Individuals with intellectual disability, developmental delay, or autism spectrum disorder;
    2. Women with primary ovarian insufficiency under the age of 40 years in whom fragile X-associated primary ovarian insufficiency is suspected;
    3. Individuals with neurologic symptoms consistent with fragile X-associated tremor or ataxia syndrome.
  - B. Individuals who have a personal or family history of FXS who are seeking reproductive counseling, including:
    1. Individuals who have a family history of FXS or a family history of undiagnosed intellectual disability;
    2. Affected individuals or relatives of affected individuals who have had a positive cytogenetic fragile X test result who are seeking information on carrier status;
    3. Prenatal testing of fetuses of known carrier mothers.
  
- II. Genetic testing for *FMR1* variants is **investigational** for all other uses.

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

## Policy Guidelines

Physical and behavioral characteristics of fragile X syndrome (FXS) include typical facial features, such as an elongated face with a prominent forehead, protruding jaw, and large ears. Connective tissue anomalies include hyperextensible finger and thumb joints, hand calluses, velvet-like skin, flat feet, and mitral valve prolapse. The characteristic appearance of adult males includes macroorchidism. Patients may show behavioral problems including autism spectrum disorder, sleeping problems, social anxiety, poor eye contact, mood disorders, and hand-flapping or biting. Another prominent feature of the disorder is neuronal hyperexcitability, manifested by hyperactivity, increased sensitivity to sensory stimuli, and a high incidence of epileptic seizures.

### Testing Strategy

Detection of CGG triplet repeats in the fragile X mental retardation 1 gene (*FMR1*) gene can occur sequentially or in parallel with determination of methylation status:

- In sequential testing, detection of CGG triplet repeats in *FMR1* is performed first. If a large number of repeats (eg, >55) is detected, reflex methylation testing can be performed to determine methylation status
- In parallel testing, detection methods such as methylation-specific polymerase chain reaction allow for detection of both the size of CGG triplet repeats in *FMR1* and methylation status.

## Cytogenetic Testing

Cytogenetic testing was used before the identification of the *FMR1* gene and is significantly less accurate than the current DNA test. The method is no longer considered an acceptable diagnostic method according to the American College of Medical Genetics and Genomics standards (see Spector et al 2021).

## Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

Variant Classification	Definition
<b>Pathogenic</b>	Disease-causing change in the DNA sequence
<b>Likely pathogenic</b>	Likely disease-causing change in the DNA sequence
<b>Variant of uncertain significance</b>	Change in DNA sequence with uncertain effects on disease
<b>Likely benign</b>	Likely benign change in the DNA sequence
<b>Benign</b>	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

## Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

## Coding

See the [Codes table](#) for details.

## Description

Fragile X syndrome (FXS) is the most common inherited form of mental disability and a known genetic cause of autism. The diagnosis is made with a genetic test that determines the number of CGG repeats in the fragile X mental retardation 1 gene (*FMR1*). *FMR1* variant testing has been investigated in a variety of clinical settings, including the evaluation of individuals with a personal or family history of intellectual disability, developmental delay, or autism spectrum disorder and in reproductive decision-making in individuals with known *FMR1* variants or positive cytogenetic fragile X testing. *FMR1* variants also cause premature ovarian failure and a neurologic disease called fragile X-associated ataxia or tremor syndrome.

### Summary of Evidence

For individuals who have characteristics of Fragile X syndrome (FXS) or an FXS-associated disorder, the evidence includes studies evaluating the clinical validity of fragile X mental retardation 1 gene (*FMR1*) variant testing. Relevant outcomes are test accuracy, test validity, and resource utilization.

The evidence demonstrates that *FMR1* variant testing can establish a definitive diagnosis of FXS and fragile X-related syndromes when the test is positive for a pathogenic variant. Following a definitive diagnosis, the treatment of comorbid conditions may be improved. At a minimum, providing a diagnosis eliminates the need for further diagnostic workup. A chain of evidence supports improved outcomes following *FMR1* variant testing. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a personal or family history of FXS who are seeking reproductive counseling, the evidence includes studies evaluating the clinical validity of *FMR1* variant testing and the effect on reproductive decisions. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision-making. Testing the repeat region of the *FMR1* gene in the context of reproductive decision-making may include: 1) individuals with either a family history of FXS or a family history of undiagnosed intellectual disability, 2) fetuses of known carrier mothers, or 3) affected individuals or their relatives who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives.

DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

### Additional Information

Not applicable.

## Related Policies

- Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

## Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member's health services 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 law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

## Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The Xpansion Interpreter test is available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. Until 2020, the FDA had chosen not to require any regulatory review of this test.

In February 2020, AmpliX Fragile X Dx and Carrier Screen Kit (Asuragen) was granted a de novo 510(k) classification by the FDA.<sup>10,11</sup> The new classification applies to this device and substantially equivalent devices of this generic type. AmpliX Fragile X Dx and Carrier Screen Kit is cleared for diagnosis of FXS in conjunction with family history and clinical signs and symptoms. The test may also be used for carrier testing, but it is not indicated for fetal diagnostic testing, the screening of eggs obtained for in vitro fertilization prior to implantation, or stand alone diagnoses of FXS. AmpliX quantifies the number of CGG repeats in the *FMR1* alleles using PCR with gene-specific and triplet repeat primers followed by size resolution with capillary electrophoresis.

## Rationale

### Background

#### Diagnosis of Fragile X Syndrome

DNA studies are used to test for fragile X syndrome (FXS). Cytogenetic testing was used before the identification of the fragile X mental retardation 1 (*FMR1*) gene and is significantly less accurate than the current DNA test. Genotypes of individuals with symptoms of FXS and individuals at risk for carrying the variant can be determined by examining the size of the trinucleotide repeat segment and the methylation status of the *FMR1* gene. Two main approaches are used: polymerase chain reaction (PCR) and Southern blot analysis.

The PCR analysis uses flanking primers to amplify a fragment of DNA spanning the repeat region.

Thus, the sizes of PCR products are indicative of the approximate number of repeats present in each allele of the individual being tested. The efficiency of PCR is inversely related to the number of CGG repeats, so large mutations are more difficult to amplify and may fail to yield a detectable product in the PCR assay. This and the fact that no information is obtained about *FMR1* methylation status are limitations of the PCR approach. On the other hand, PCR analysis permits accurate sizing of alleles in the normal zone, the "gray zone," and premutation range on small amounts of DNA in a relatively short turnaround time. Also, the assay is not affected by skewed X-chromosome inactivation.<sup>1,2</sup>

The difficulty in fragile X testing is the high fraction of GC bases in the repeat region makes it extremely difficult for standard PCR techniques to amplify beyond 100 to 150 CGG repeats.

Consequently, Southern blot analysis is commonly used to determine the number of triplet repeats in FXS and methylation status. Alternatives to Southern blotting for determining *FMR1* methylation status have been developed. These include methylation-sensitive PCR and methylation-specific melting curve analysis.<sup>3,4,5,6</sup> One test currently available in Europe (FastFraX; TNR Diagnostics, Singapore) combines a direct triplet repeat-primed PCR with melting curve analysis for detecting CGG expansions.<sup>7</sup> Asuragen offers the Xpansion Interpreter<sup>®</sup> test, which analyzes AGG sequences that interrupt CGG repeats and may stabilize alleles, protecting against expansion in subsequent

generations.<sup>8,9</sup> Asuragen also markets AmpliX<sup>®</sup> Fragile X Dx and Carrier Screen Kit, which is the first test approved by the U.S. Food and Drug Administration (FDA) (see Regulatory Status).<sup>10</sup>

In 2011, a panel of genotyping reference materials for FXS was developed and is expected to be stable over many years and available to all diagnostic laboratories. A panel of 5 genomic DNA samples (normal female, female premutation, male premutation, male full mutation, and female full mutation) was endorsed by the European Society of Human Genetics and approved as an International Standard by the Expert Committee on Biological Standardization at the World Health Organization.

### **Treatment**

Current approaches to therapy are supportive and symptom-based. Psychopharmacologic intervention to modify behavioral problems in a child with FXS may represent an important adjunctive therapy when combined with other supportive strategies including speech therapy, occupational therapy, and special education services. Medication management may be indicated to modify attention deficits, impaired impulse control, and hyperactivity. Anxiety-related symptoms, including obsessive-compulsive tendencies with perseverative behaviors, also may be present and require medical intervention. Emotional lability and episodes of aggression and self-injury may be a danger to the child and others around him or her; therefore, the use of medication(s) to modify these symptoms also may significantly improve an affected child's ability to participate more successfully in activities in the home and school settings.

### **Literature Review**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test.

The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

### **Individuals With Characteristics of a Fragile X Syndrome or a Fragile X–Associated Disorder**

Fragile X syndrome (FXS) is the most common cause of heritable intellectual disability, characterized by moderate intellectual disability in males and mild intellectual disability in females. FXS affects approximately 1 in 4000 males and 1 in 8000 females. In addition to intellectual impairment, patients present with typical facial features, such as an elongated face with a prominent forehead, protruding jaw, and large ears. Connective tissue anomalies include hyperextensible finger and thumb joints, hand calluses, velvet-like skin, flat feet, and mitral valve prolapse. The characteristic appearance of adult males includes macroorchidism. Patients may show behavioral problems including autism spectrum disorders, sleeping problems, social anxiety, poor eye contact, mood disorders, and hand-flapping or biting. Another prominent feature of the disorder is neuronal hyperexcitability, manifested by hyperactivity, increased sensitivity to sensory stimuli, and a high incidence of epileptic seizures.

Fragile X syndrome is associated with the expansion of the CGG trinucleotide repeat in the fragile X mental retardation 1 (*FMR1*) gene on the X chromosome. The syndrome is associated with the expansion of the *FMR1* gene CGG triplet repeat above 200 units in the 5' untranslated region of *FMR1*, leading to hypermethylation of the promoter region followed by transcriptional inactivation of the gene. Fragile X syndrome is caused by a loss of the fragile X mental retardation protein, which is believed to play a key role in early brain development and brain function.

### Fragile X–Associated Disorders

Patients with a premutation (55 to 200 CGG repeats) may develop an *FMR1*-related disorder, such as fragile X-associated tremor or ataxia syndrome or, in women, fragile X-associated premature ovarian insufficiency. Fragile X-associated tremor or ataxia syndrome is a late-onset syndrome, comprising progressive development of intention tremor and ataxia, often accompanied by progressive cognitive and behavioral difficulties, including memory loss, anxiety, reclusive behavior, deficits of executive function, and dementia. Fragile X-associated premature ovarian insufficiency is characterized by ovarian failure before 40 years of age.

### Clinical Context and Test Purpose

Diagnosis of FXS may include a genetic test that determines the number of CGG repeats in the fragile X gene. The patient is classified as normal, intermediate (“gray zone”), premutation, or full mutation based on the number of CGG repeats (Table 1).<sup>12</sup> Approximately 1% to 3% of children initially diagnosed with autism are shown to have FXS, with the expansion of the CGG trinucleotide repeat in the *FMR1* gene to full mutation length.<sup>13</sup> A considerable number of children evaluated for autism have been found to have an *FMR1* premutation (55 to 200 CGG repeats).<sup>14</sup> Fragile X-associated disorders (fragile X-associated premature ovarian insufficiency and fragile X-associated tremor or ataxia) are associated with an *FMR1* premutation (55 to 200 CGG repeats).

**Table 1. Classifications of CGG Repeat Length**

Mutation Classification	CGG Repeat Length	Methylation Status	Variant Classification
Full mutation	>200 to 230	Methylated	Pathogenic variant
Premutation	55 to 200	Unmethylated	Pathogenic variant
Intermediate	45 to 54	Unmethylated	Uncertain variant
Normal	5 to 44	Unmethylated	Benign variant

The purpose of *FMR1* variant testing in individuals who have characteristics of FXS or a fragile X-associated disorder is to provide an accurate diagnosis and improve treatment of the associated behavioral and medical conditions.

The following PICO was used to select literature to inform this review.

### Populations

The relevant population of interest is:

- Individuals with characteristics of FXS or a fragile X-associated disorder including:
  - Individuals of either sex with intellectual disability, developmental delay, or autism spectrum disorder.
  - Women with primary ovarian failure under the age of 40 years in whom fragile X-associated premature ovarian insufficiency is suspected.
  - Individuals with neurologic symptoms consistent with fragile X-associated tremor or ataxia syndrome.

### Interventions

The relevant interventions of interest are testing for *FMR1* variant and methylation status.

### Comparators

Standard clinical evaluation without genetic testing is used to diagnose FXS or a fragile X-associated disorder.

### Outcomes

The general outcomes of interest are an accurate diagnosis of individuals with FXS or fragile X-associated disorders and improved management of the disorder. This test would be performed when characteristics of FXS or fragile X-associated disorders are identified.

### Study Selection Criteria

For the evaluation of clinical validity of the test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

### Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

### Review of Evidence

Clinical sensitivity and specificity are 99% for premutation and full variant alleles. Although diagnostic errors can occur due to rare sequence variations, CGG repeat expansion full mutations account for more than 99% of cases of FXS.<sup>2</sup> Therefore, tests that measure the CGG repeat region of the *FMR1* gene are clinically valid. Tests have been shown to be more than 99% sensitive. Positive results are 100% specific. There are no known forms of fragile X mental retardation protein deficiency that do not map to the *FMR1* gene.

### Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

The conditions caused by abnormal CGG repeats in the *FMR1* gene— fragile X-associated tremor or ataxia syndrome and fragile X-associated premature ovarian insufficiency— do not have specific treatments that alter the natural history of the disorders. However, because they represent relatively common causes of conditions that are often difficult to diagnose and involve numerous diagnostic tests, the capability of *FMR1* testing to obtain an accurate, definitive diagnosis and avoid additional diagnostic testing supports its clinical utility. The knowledge that the condition is caused by variants of *FMR1* provides important knowledge for offspring and for assessing the risk of disease in subsequent generations.

Also, FXS is associated with a number of medical and behavioral comorbidities.<sup>15</sup> Behavioral comorbidities may include attention problems, hyperactivity, anxiety, aggression, poor sleep, and self-injury. Individuals with FXS are also prone to seizures, recurrent otitis media, strabismus, gastrointestinal disturbances, and connective tissue problems. A correct diagnosis can lead to the appropriate identification and treatment of these comorbidities.

### Section Summary: Individuals with Characteristics of a Fragile X Syndrome or a Fragile X-Associated Disorder

The evidence demonstrates that *FMR1* variant testing can establish a definitive diagnosis of FXS and fragile X-related disorders when the test is positive for a pathogenic variant. Following a definitive diagnosis, the treatment of comorbid conditions may be improved. At a minimum, providing a diagnosis eliminates the need for further diagnostic workup.

### Individuals With a Personal or Family History of Fragile X Syndrome Who Are Seeking Reproductive Counseling

#### Clinical Context and Test Purpose

Premutation alleles (55 to 200 CGG repeats) in females are unstable and may expand to full mutations in offspring. Premutations of fewer than 59 repeats have not been reported to expand to a

full mutation in a single generation. Premutation alleles in males may expand or contract by several repeats with the transmission; however, expansion to full mutations has not been reported.

Premutation allele prevalence in whites is approximately 1 in 1000 males and 1 in 350 females.<sup>1,16,17</sup> Full mutations are typically maternally transmitted. The mother of a child with an *FMR1* variant is almost always a carrier of a premutation or full mutation. Women with a premutation carry a 50% risk of transmitting an abnormal gene, which contains either a premutation copy number (55 to 200) or a full mutation (>200) in each pregnancy.

Men who are premutation carriers are referred to as transmitting males. All of their daughters will inherit a premutation, but their sons will not inherit the premutation. Males with a full mutation usually have an intellectual disability and decreased fertility.

The purpose of *FMR1* testing in individuals who have a personal or family history of FXS is to inform reproductive decision-making.

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is:

- Individuals who have a personal or family history of FXS who are seeking reproductive counseling including:
  - Individuals seeking reproductive counseling who have a family history of FXS or a family history of undiagnosed intellectual disability.
  - Affected individuals or relatives of affected individuals who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status.
  - Prenatal testing of fetuses of known carrier mothers.

### ***Interventions***

The relevant intervention of interest is testing for *FMR1* variant status.

### ***Comparators***

Standard clinical evaluation without genetic testing is currently being used for reproductive decision-making.

### ***Outcomes***

The general outcome of interest is reproductive decision-making. The timing of the test is when the individual is making reproductive decisions.

### **Study Selection Criteria**

For the evaluation of clinical validity of the test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

### **Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

## Review of Evidence

The inheritance patterns of the *FMR1* gene have been well characterized, and the penetrance of the fragile X-associated disorders is very high.

## Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Hersh and Saul (2011) reported on families with an affected male and whether an early diagnosis would have influenced their reproductive decision-making.<sup>17</sup> After a diagnosis in the affected male was made, 73% of families reported that the diagnosis of FXS affected their decision to have another child, and 43% of the families surveyed had a second child with a full mutation. LePoulenec et al (2024) reported on pregnancy outcomes in women with *FMR1* gene premutations.<sup>18</sup> Before the premutations were found, the 63 affected women had 20 live births. Of these 20, 7 children were diagnosed with FXS. After the diagnosis of the gene premutation, these women had 23 pregnancies, 18 of which led to a diagnosis of FXS. The authors concluded that genetic counseling about the possibility of transmitting FXS genes is needed, along with education about the opportunity to seek preimplantation or prenatal diagnosis.

## Section Summary: Individuals With a Personal or Family History of Fragile X Syndrome Who Are Seeking Reproductive Counseling

Testing the repeat region of the *FMR1* gene in the context of reproductive decision-making may include: 1) individuals with either a family history of FXS or a family history of undiagnosed intellectual disability, 2) fetuses of known carrier mothers, or 3) affected individuals or their relatives who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women.

## Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

## American College of Medical Genetics and Genomics

In 2005, the American College of Medical Genetics and Genomics (ACMG) made the following recommendations on diagnostic and carrier testing for fragile X syndrome (FXS).<sup>2</sup> The purpose of these recommendations was to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the fragile X mental retardation 1 (*FMR1*) gene.

- "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 intellectual disability.
- 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 before 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.”

In the clinical genetics evaluation to identify the etiology of autism spectrum disorders, ACMG recommended testing for FXS as part of the first-tier testing.<sup>13</sup>

According to the ACMG recommendations, the following is the preferred approach to testing:<sup>2</sup>

- “DNA analysis is the method of choice if one is testing specifically for fragile X syndrome (FXS) and associated trinucleotide repeat expansion in the *FMR1* gene.”
- “For isolated cognitive impairment, DNA analysis for FXS should be performed as part of a comprehensive genetic evaluation that includes routine cytogenetic evaluation. Cytogenetic studies are critical since constitutional chromosome abnormalities have been identified as frequently or more frequently than fragile X mutations in mentally retarded individuals referred for fragile X testing.”
- Fragile X testing is not routinely warranted for children with isolated attention-deficit/hyperactivity disorder (see Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement, & Steering Committee on Quality Improvement Management, 2011).
- “For individuals who are at risk due to an established family history of fragile X syndrome, DNA testing alone is sufficient. If the diagnosis of the affected relative was based on previous cytogenetic testing for fragile X syndrome, at least one affected relative should have DNA testing.”
- “Prenatal testing of a fetus should be offered when the mother is a known carrier to determine whether the fetus inherited the normal or mutant *FMR1* gene. Ideally, DNA testing should be performed on cultured amniocytes obtained by amniocentesis after 15 weeks’ gestation. DNA testing can be performed on chorionic villi obtained by CVS [chorionic villous sampling] at 10 to 12 weeks’ gestation, but the results must be interpreted with caution because the methylation status of the *FMR1* gene is often not yet established in chorionic villi at the time of sampling. A follow-up amniocentesis may be necessary to resolve an ambiguous result.”
- “If a woman has ovarian failure before the age of 40, DNA testing for premutation size alleles should be considered as part of an infertility evaluation and prior to in vitro fertilization.”
- “If a patient has cerebellar ataxia and intentional tremor, DNA testing for premutation size alleles, especially among men, should be considered as part of the diagnostic evaluation.”

The ACMG made recommendations on diagnostic and carrier testing for FXS to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the *FMR1* gene. These recommendations included testing of individuals of either sex who have intellectual disability, developmental delay, or autism spectrum disorder, especially if they have any physical or behavioral characteristics of FXS.<sup>2</sup>

In 2021, the ACMG released a revised technical standard on laboratory testing for fragile X.<sup>12</sup> The authors noted that the new laboratory standards “are in general agreement” with the 2005 ACMG policy statement summarized above.

### American Academy of Pediatrics

In 2014 (reaffirmed in 2019), the American Academy of Pediatrics recommended that fragile X testing is performed in any child who presents with global developmental delay or intellectual disability without a specific etiology.<sup>19</sup> *FMR1* testing for CGG repeat length is considered a first-line test by the Academy and will identify 2% to 3% of boys with global developmental delay/intellectual disability and 1% to 2% of girls (full mutation).

### American College of Obstetricians and Gynecologists

In 2017 (reaffirmed in 2023), the American College of Obstetricians and Gynecologists recommended that screening for FXS be offered to women with a family history suggestive of FXS and to women with a medical history suggestive of being a fragile X carrier (ie, ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years).<sup>20</sup> The College recommended prenatal diagnostic testing for FXS to known carriers of the fragile X premutation or full mutation.

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in November 2024 did not identify any ongoing or unpublished trials that would likely influence this review.

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### Documentation for Clinical Review

**Please provide the following documentation:**

- **History and physical and/or consultation notes including:**
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history, if applicable
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
  - Consultation and medical clearance report(s), when applicable
  - Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
  - Laboratory results
  - Other pertinent multidisciplinary notes/reports: (i.e., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management), when applicable

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

- Results/reports of tests performed
- Procedure report(s)

### Coding

*The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.*

Type	Code	Description
CPT®	81243	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81244	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and methylation status)
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
03/01/2017	BCBSA Medical Policy adoption
03/01/2018	Policy title change from Genetic Testing for FMR1 Mutations (Including Fragile X Syndrome) Policy revision without position change
03/01/2019	Policy revision without position change
11/01/2025	Policy reactivated. Previously archived from 05/01/2020 to 10/31/2025

### Definitions of Decision Determinations

**Healthcare Services:** For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

**Medically Necessary:** Healthcare 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 of California, are: (a) consistent with Blue Shield of California 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 member; 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 or Experimental:** Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

- A. The technology must have final approval from the appropriate government regulatory bodies.
  - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
  - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
  - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.
- B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

- The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
  - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.
- C. The technology must improve the net health outcome.
- The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.
- D. The technology must be as beneficial as any established alternatives.
- The technology should improve the net health outcome as much as, or more than, established alternatives.
- E. The improvement must be attainable outside the investigational setting.
- When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

## Feedback

Blue Shield of California is 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. Our medical policies are available to view or download at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

For medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

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](http://www.blueshieldca.com/provider).

*Disclaimer: 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 member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

Appendix A

POLICY STATEMENT	
BEFORE	AFTER
<p>Reactivated Policy</p> <p>Policy Statement: N/A</p>	<p><u>Blue font: Verbiage Changes/Additions</u></p> <p><b>Genetic Testing for FMRI Variants (Including Fragile X Syndrome) 2.04.83</b></p> <p>Policy Statement:</p> <ol style="list-style-type: none"> <li>I. Genetic testing for fragile X mental retardation 1 gene (<i>FMRI</i>) variants may be considered <b>medically necessary</b> for <b>any</b> of the following populations:                     <ol style="list-style-type: none"> <li>A. Individuals with characteristics of fragile X syndrome (FXS) or a fragile X-associated disorder, including:                             <ol style="list-style-type: none"> <li>1. Individuals with intellectual disability, developmental delay, or autism spectrum disorder;</li> <li>2. Women with primary ovarian insufficiency under the age of 40 years in whom fragile X-associated primary ovarian insufficiency is suspected;</li> <li>3. Individuals with neurologic symptoms consistent with fragile X-associated tremor or ataxia syndrome.</li> </ol> </li> <li>B. Individuals who have a personal or family history of FXS who are seeking reproductive counseling, including:                             <ol style="list-style-type: none"> <li>1. Individuals who have a family history of FXS or a family history of undiagnosed intellectual disability;</li> <li>2. Affected individuals or relatives of affected individuals who have had a positive cytogenetic fragile X test result who are seeking information on carrier status;</li> <li>3. Prenatal testing of fetuses of known carrier mothers.</li> </ol> </li> </ol> </li> <li>II. Genetic testing for <i>FMRI</i> variants is <b>investigational</b> for all other uses.</li> </ol>