Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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*Current Policy Effective Date: 5/1/24
(See policy history boxes for previous effective dates)

Title: Genetic Testing for FMR1 and FMR2 Variants (Including Fragile X and Fragile XE Syndromes)

Description/Background

Diagnosis of Fragile X Syndrome

DNA studies are used to test for fragile X syndrome (FXS). Cytogenetic testing was used before 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 methylation status of the *FMR1* gene. Two main approaches are used: polymerase chain reaction (PCR) and Southern blot analysis.

Polymerase chain reaction 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.[1,2]

The difficulty in fragile X testing is that 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. They include methylation-sensitive PCR and methylation-specific melting curve analysis.[3,4,5,6] 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.[7] Asuragen offers the Xpansion Interpreter® test, which analyzes AGG sequences that interrupt CGG repeats and may stabilize alleles, protecting against expansion in subsequent generations.[8,9] Asuragen also markets

AmplideX® 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).[10]

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.

Individuals With Characteristics of a Fragile X Syndrome or a Fragile X-Associated Disorder

Fragile X syndrome 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. FXS 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 (55-200 CGG repeats) may develop an *FMR1*-related disorder, such as fragile X-associated tremor or ataxia syndrome or, in , 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.

Fragile XE Syndrome (FRAXE)
Fragile XE syndrome is caused by variants in the *FMR2* (or *AFF2*) gene, which is located in close proximity to the *FMR1* gene. When performing preliminary cytogenetic tests, variants in this gene appear similarly to the "fragile" area that is found in FXS.

Estimates of prevalence of fragile XE syndrome range from 1 in 25,000 to 1 in 100,000. Reported clinical features include mild to borderline intellectual disabilities, learning difficulties, speech delays and developmental delay. Some individuals also display autistic behaviors such as repetitive behaviors, intense interest in a particular subject and hand flapping. Symptoms vary from person to person and there are no consistent physical characteristics associated with fragile XE syndrome.

Molecular variants found in the *AFF2* gene include a CCG trinucleotide repeat of more than 200 times. Rarely, small deletions of genetic material from the *AFF2* gene are also associated with fragile XE syndrome. The structure of the *AFF2* gene has been characterized; however, the scope of its function is not yet known. [11,12,13,21]

Regulatory Status:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. 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 U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In February 2020, AmplideX® Fragile X Dx and Carrier Screen Kit (Asuragen) was granted a de novo 510(k) classification by the FDA.[10,14] The new classification applies to this device and substantially equivalent devices of this generic type. AmplideX® 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. AmplideX® 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.

Medical Policy Statement

Genetic testing for *FMR1* variants may be considered established in select individual populations.

Genetic testing for *FMR2* variants (*AFF2* gene) is considered experimental/ investigational. The medical literature has not demonstrated the clinical utility of this testing.

Inclusionary and Exclusionary Guidelines

***FMR1* Gene Testing**

Inclusions:

Individuals with characteristics of fragile X syndrome or a fragile X-associated disorder, including:

- Individuals with intellectual disability, developmental delay, or autism spectrum disorder
- Women with primary ovarian insufficiency under the age of 40 in whom fragile X-associated primary ovarian insufficiency is suspected
- Women with ovarian failure before the age of 40 prior to in vitro fertilization (refer to member's specific certificate for coverage of in-vitro services)
- Individuals with neurologic symptoms consistent with fragile X-associated tremor or ataxia syndrome.

Individuals who have a personal or family history of fragile X syndrome who are seeking reproductive counseling, including:

- Individuals who have a family history of fragile-X syndrome 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 information on carrier status
- Prenatal testing of fetuses of known carrier mothers.

Exclusions:

Genetic testing for *FMR1* variants for all other uses not specified under the inclusions.

Genetic testing for *FMR2 (AFF2*) variants is considered experimental / investigational.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

81243 81244

Other codes (investigational, not medically necessary, etc.):

81171 81172

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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

Diagnosis of fragile X syndrome (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).[15] Approximately 1% to 3% of children initially diagnosed with autism are shown to have FXS, with expansion of the CGG trinucleotide repeat in the *FMR1* gene to full mutation length.[16] A considerable number of children evaluated for autism have been found to have a *FMR1* premutation (55-200 CGG repeats).[17] Fragile X-associated disorders (fragile X associated premature ovarian insufficiency and fragile X-associated tremor or ataxia) are associated with a *FMR1* premutation (55-200 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

Clinical Context and Test Purpose

The purpose of *FMR1* variant testing in patients 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 question addressed in this evidence review is: Does *FMR1* variant testing in patients with conditions or family history consistent with the presence of a pathogenic *FMR1* variant (eg, premutation or mutation) improve health outcomes?

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 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 patients 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.[2] 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The conditions caused by abnormal CGG repeats in the *FMR1* gene - FXS, 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.[18] 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 an FXS 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, 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 (55-200 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.[1,,19,20] 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 (55-200) 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 patients who have a personal or family history of FXS is to inform reproductive decision making.

The question addressed in this evidence review is: Does *FMR1* testing in this population improve health outcomes?

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
Methodologically credible studies were selected using the principles described in the first indication.

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Hersh and Saul (2011)[20] reported on families with an affected male and whether an early diagnosis would have influenced their reproductive decision making. 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 had a second child with a full mutation.

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 individuals with either a family history of FXS or a family history of undiagnosed intellectual disability, fetuses of known carrier mothers, or 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.

SUMMARY OF EVIDENCE

For individuals who have characteristics of FXS or an FXS-associated disorder, the evidence includes studies evaluating the clinical validity of *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, 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 a meaningful 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 a meaningful improvement in the net health outcome.

Fragile XE Syndrome

OMIM review reports Allingham-Hawkins and Ray (1995) examined 300 developmentally delayed males, referred for fragile X testing but negative for the *FMR1* gene trinucleotide expansion. They were then tested for the FRAXE expansion. The group had a wide range of intellectual or behavioral problems. None of the patients tested positive for the FRAXE expansion. These results suggested that FRAXE is not a common etiologic factor in this group of patients.

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[2], the American College of Medical Genetics and Genomics (ACMG) made the following recommendations on diagnostic and carrier testing for fragile X syndrome (FXS). The purpose of these recommendations is to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the *FMR1* gene.

- "Individuals of either sex with intellectual disability, 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 intellectual disability.
- 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 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."

In the clinical genetics evaluation in identifying the etiology of autism spectrum disorders, the ACMG recommended testing for FXS as part of first-tier testing.[16]

According to ACMG recommendations, the following is the preferred approach to testing:[2]

- "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 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.[2]

In 2021, the ACMG released a revised technical standard on laboratory testing for fragile X.[15] 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, the 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.[21] *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 2020)[22], 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). 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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations
National:
There is no national coverage determination (NCD) on this topic. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Local:
Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding: MolDX: Fragile X (A55163)
Original Effective Date: 02/16/2017 Revision Effective Date: 11/25/2021

Effective for dates of service on and after 01/1/2013

The MolDX Team has determined that Fragile X testing is not a Medicare covered service. Screening in the absence of signs and symptoms of an illness or injury is not defined as a Medicare benefit. Therefore, MolDX will deny testing for Fragile X as a statutorily excluded service.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing - Chromosomal Microarray (CMA) Analysis and Next-Generation Sequencing Panels, for the Evaluation of Children with Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and/or Congenital Anomalies

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24. WPS Medicare, Local Coverage Article: Billing and Coding: MolDX: Fragile X (A55163). https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=55163&ver=14&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=BC%7cSAD%7cRTC%7cReg&PolicyType=Both&s=27&KeyWord=81243&KeyWordLookUp=Doc&KeyWordSearchType=Exact&kq=true&bc=EAAAABAAAAAA& Accessed 11/23/23.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/23/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/14	101513	10/25/13	Joint policy established
11/1/15	8/24/15	9/14/15	Routine maintenance

11/1/16	8/16/16	8/16/16	Routine maintenance
9/1/17	6/20/17	6/20/17	Routine maintenance Reworded inclusion regarding ataxia and tremor. Updated local Medicare information. WPS GHA has determined that testing for the genes/gene components represented by procedure codes 81243 and 81244 do not meet the Medicare criteria for a covered service.
9/1/18	6/19/18	6/19/18	Routine maintenance Rationale and criteria revised
9/1/19	6/18/19		Codes 81171, 81172 added; title of policy changed. Description updated to include FMR2. Routine maintenance
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		Routine maintenance
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance (jf) Vendor Managed: NA
5/1/24	2/20/24		2024 Code Update (jf) CPT Code Update: 81171, 81172, 81243, 81244 The nomenclature code description are being revised to comply with federal law around references to intellectual disabilities. In addition, the Molecular Pathology guidelines specify that genes in the code set are identified by the HUGO-approved full gene names. • Vendor Managed: NA

Next Review Date: 2nd Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR FMR1 AND FMR2 VARIANTS (INCLUDING FRAGILE X AND FRAGILE XE SYNDROMES)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.