

| 2.04.83 Genetic Testing for FMR1 Variants (Including Fragile X Syndrome) | | | |
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| Section: | 2.0 Medicine | Page: | Page 1 of 14 |

Policy Statement

Genetic testing for *FMR1* variants may be considered **medically necessary** for **any** of the following patient populations:

- Individuals with characteristics of fragile X syndrome or a fragile X-associated disorder, including:
 - Individuals with intellectual disability, developmental delay, or autism spectrum disorder
 - Individuals with neurologic symptoms consistent with fragile X-associated tremor or ataxia syndrome
 - Women with primary ovarian insufficiency under the age of 40 in whom fragile X-associated primary ovarian insufficiency is suspected
- Individuals who have a personal or family history of fragile X syndrome who are seeking reproductive counseling, including:
 - Affected individuals or relatives of affected individuals who have had a positive cytogenetic fragile X test result who are seeking information on carrier status
 - Individuals who have a family history of fragile X syndrome or a family history of undiagnosed intellectual disability
 - Prenatal testing of fetuses of known carrier mothers

Genetic testing for *FMR1* variants is considered **investigational** for **all** other uses.

Policy Guidelines

Physical and behavioral characteristics of fragile X syndrome (FXS) include typical facial features, such as an elongated face with 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 *FMR1* gene can occur sequentially or in parallel with determination of methylation status:

1. In sequential testing, detection of CGG triplet repeats in *FMR1* is performed first. If a large number of repeats (e.g., >55) is detected, reflex methylation testing can be performed to determine methylation status
2. 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 American College of Medical Genetics and Genomics (ACMG) standards (see Monaghan et al, 2013).

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

There are specific CPT codes for this testing:

- **81243:** *FMR1 (fragile X mental retardation 1)* (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
- **81244:** *FMR1 (fragile X mental retardation 1)* (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status)

Note: CPT code 81243 is used for polymerase chain reaction testing of CGG triplet repeats in *FMR1*. If a large number of repeats (e.g., >55) is detected, reflex methylation testing (CPT code 81244) can further characterize abnormal alleles (e.g., to differentiate premutation from full mutation alleles).

Description

Fragile X syndrome (FXS) is the most common inherited form of mental disability and known genetic cause of autism. The diagnosis is made with a genetic test that determines the number of CGG repeats in the fragile X gene, *FMR1*. *FMR1* variant testing has been investigated in a variety of clinical settings, including in 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.

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

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

Regulatory Status

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. The Xpansion Interpreter® test is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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}

Rationale

Background Fragile X

Fragile X Syndrome

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 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 (FXS) is associated with the expansion of the CGG trinucleotide repeat in the fragile X mental retardation 1 (*FMR1*) gene on the X chromosome. FXS 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 women, fragile X–associated premature ovarian insufficiency (FXPOI). 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. FXPOI is characterized by ovarian failure before the 40 years of age.

Diagnosis

DNA studies are used to test for FXS. Cytogenetic testing was used before identification of the *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.

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.^{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.³⁻⁶ 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

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

See Appendix Table 1 for genetic testing categories.

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 Clinical Context and Test Purpose

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 (see Table 1).¹ 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.¹⁰ A considerable number of children evaluated for autism have been found to have a *FMR1* premutation (55-200 CGG repeats).¹¹ Fragile X-associated disorders (fragile X associated premature ovarian insufficiency [FXPOI] 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 |

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 (e.g., premutation or mutation) improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are:

- 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 FXPOI 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.

Timing

This test would be performed when characteristics of FXS or fragile X–associated disorders are identified.

Setting

A number of laboratories can assess for the *FMR1* variant and methylation status.

Simplifying Test Terms

There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or predicting a response to therapy.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

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.¹² 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 Who Have a Personal or Family History of FXS 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.^{1,13,14} 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 PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are:

- 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.

Timing

The timing of the test is when the individual is making reproductive decisions.

Setting

A number of laboratories can perform testing for the *FMR1* variant and methylation status.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist.

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).

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) reported on families with an affected male and whether an early diagnosis would have influenced their reproductive decision making.¹⁴ 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 Who Have a Personal or Family History of FXS 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 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG) made the following recommendations in 2005 on diagnostic and carrier testing for fragile X syndrome (FXS).² The purpose of these recommendations was to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the *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.¹⁰

According to ACMG recommendations, the following is the preferred approach to testing²:

- "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.”

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

Academy of Pediatrics

The Academy of Pediatrics (2014) recommended that fragile X testing be performed in any child who presents with global developmental delay or intellectual disability without a specific etiology.¹⁵ *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, 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 (i.e., ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40).¹⁶ The College recommended prenatal diagnostic testing for FXS to known carriers of the fragile X premutation or full mutation.

European Molecular Genetics Quality Network

In 2015, the European Molecular Genetics Quality Network issued best practice guidelines for the molecular genetic testing and reporting of FXS, fragile X–associated primary ovarian insufficiency, and fragile X–associated tremor or ataxia syndrome.¹⁷ The guidelines recommended, “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.” Technical limitations of specific techniques, such as Southern blot and polymerase chain reaction–based methods, were described.

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 December 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

Appendix

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.83

| Category | Addressed |
|---|-----------|
| 1. Testing of an affected individual's germline to benefit the individual | |
| 1a. Diagnostic | X |
| 1b. Prognostic | |
| 1c. Therapeutic | |
| 2. Testing cancer cells from an affected individual to benefit the individual | |
| 2a. Diagnostic | |
| 2b. Prognostic | |
| 2c. Therapeutic | |
| 3. Testing an asymptomatic individual to determine future risk of disease | |
| 4. Testing of an affected individual's germline to benefit family members | |
| 5. Reproductive testing | |
| 5a. Carrier testing: preconception | X |
| 5b. Carrier testing: prenatal | X |
| 5c. In utero testing: aneuploidy | |
| 5d. In utero testing: familial variant | X |
| 5e. In utero testing: other | |
| 5f. Preimplantation testing with in vitro fertilization | |

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- 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

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

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

| Type | Code | Description |
|------------------|---------------|--|
| CPT® | 81243 | FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles |
| | 81244 | FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status) |
| HCPCS | None | |
| ICD-10 Procedure | None | |
| ICD-10 Diagnosis | All Diagnoses | |

Policy History

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

| Effective Date | Action | Reason |
|----------------|---|--------------------------|
| 03/01/2017 | BCBSA Medical Policy adoption | Medical Policy Committee |
| 03/01/2018 | Policy title change from Genetic Testing for FMR1 Mutations (Including Fragile X Syndrome) Policy revision without position change | Medical Policy Committee |

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

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

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

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

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