BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.83 Genetic Testing for FMR1 Variants (Including Fragile X Syndrome)

Annual Effective Policy Date: April 1, 2024

Original Policy Date: September 2012

Related Policies:

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

Genetic Testing for FMR1 Variants (Including Fragile X Syndrome)

Description

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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.

OBJECTIVE

The objective of this evidence review is to evaluate whether fragile X mental retardation 1 gene (*FMR1)* variant testing improves health outcomes in individuals with conditions or family history consistent with the presence of a pathogenic *FMR1* variant (eg, premutation or mutation).

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POLICY STATEMENT

Genetic testing for fragile X mental retardation 1 gene (*FMR1)* variants may be considered **medically necessary** for the following populations:

- Individuals with characteristics of fragile X syndrome (FXS) 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;
    - Individuals with neurologic symptoms consistent with fragile X-associated tremor or ataxia syndrome.
- Individuals who have a personal or family history of FXS who are seeking reproductive counseling, including:
    - Individuals 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 information on carrier status;
    - Prenatal testing of fetuses of known carrier mothers.

Genetic testing for *FMR1* variants is **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 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.

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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
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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FDA REGULATORY STATUS

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.

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, AmplideX Fragile X Dx and Carrier Screen Kit (Asuragen) was granted a de novo 510(k) classification by the FDA.[10,11,] 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.

RATIONALE

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.

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SUPPLEMENTAL INFORMATION

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).[2,] 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.[13,]

According to the 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."

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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.[12,] 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.[18,]*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).[19,] 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2013	New policy	
December 2014	Replace policy	Policy updated with literature review; references 3-4, 6-8, 10- 15, and 17- 18, added. Policy statements and entire policy updated to reflect current DSM-V diagnostic categories, i.e., "intellectual disability, replaces "mental retardation, No change to policy statements except the addition of Genetic testing for FMR1 is investigational for all other uses.
September 2015	Replace policy	Policy updated with literature review; references 16 and 20 added. Policy statements unchanged.
December 2016	Replace policy	Policy statement unchanged
March 2017	Replace policy	Policy updated with literature review through December 5, 2016; no references added. Added fragile-X associated tremor/ataxia syndrome and FMR1-related primary ovarian failure to medically necessary indications
March 2018	Replace policy	Policy updated with literature review through November 6, 2017; references 12 and 15-16 added; "mutation, changed to "variant, where indicated. Policy statement also revised to align with FEP benefit, with the removal of genetic testing for reproductive genetic testing.
March 2019	Replace policy	Policy updated with literature review through November 1, 2018; no references added. Policy statements unchanged.
March 2020	Replace policy	Policy updated with literature review through November 11, 2019; no references added. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through November 16, 2020; no references added. Policy statements unchanged. "does not address testing for reproductive purposes" added to Objectives.
March 2022	Replace policy	Policy updated with literature review through November 12, 2021; reference added. Policy statements unchanged.
March 2023	Replace policy	Policy updated with literature review through November 13, 2022; no references added. Policy statements unchanged.
March 2024	Replace policy	Policy updated with literature review through November 20, 2023; no references added. Minor editorial refinements to policy statements; intent unchanged.

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