BlueCross BlueShield Federal Employee Program.

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

Effective Date: April 15, 2018

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

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.

FDA 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 (CLIA). The Xpansion Interpreter® test is available under the auspices of the CLIA. Laboratories that offer LDTs must be licensed by CLIA 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]

POLICY STATEMENT

Genetic testing for *FMR1* variants may be considered **medically necessary** for 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;
  - 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.

POLICY GUIDELINES

Physical and behavioral characteristics of fragile X syndrome 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 (eg, >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 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.

BENEFIT APPLICATION

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.

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

RATIONALE

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.

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.(see Policy Guidelines and Benefit Application sections*)
- Affected individuals or their relatives in the context of a positive cytogenetic fragile X test results 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." (see Policy Guidelines and Benefit Application sections*)

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 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 as 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." (see Policy Guidelines and Benefit Application sections*)

"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." (see Policy Guidelines and Benefit Application sections*)

"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 (ie, 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. (see Policy Guidelines and Benefit Application sections*)

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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY

Date	Action	Description
September 2013	New Policy	
December 2014	Update 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, ie, “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	Update Policy	Policy updated with literature review; references 16 and 20 added. Policy statements unchanged.
December 2016	Update Policy	Policy statement unchanged
March 2017	Update 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	Update Policy	Policy updated with literature review through November 6, 2017; references 12 and 15-16 added; “mutation” changed to “variant” where indicated. Policy statements related to reproductive genetic testing removed to correlate with benefit brochure language.