Genetic Testing for FMR1 Mutations Including Fragile X Syndrome

File Name: genetic_testing_for_fmr1_mutations_including_fragile_x_syndrome
Origination: 6/2012
Last CAP Review: 3/2018
Next CAP Review: 3/2019
Last Review: 3/2018

Description of Procedure or Service

Fragile X syndrome is the most common cause of heritable intellectual disability and known genetic cause of autism. The diagnosis includes use of a genetic test that determines the number of CGG repeats in the fragile X gene.

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 one in 4,000 males and one in 8,000 females. In addition to the intellectual impairment, patients present with typical facial characteristics 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.

Approximately 1-3% of children ascertained on the basis of autism diagnosis are shown to have fragile X syndrome, with expansion of the CGG trinucleotide repeat in the FMR1 gene to full mutation size of 200 or more repeats. A considerable number of children being evaluated for autism have been found to have FMR1 pre-mutations (55-200 CGG repeats.)

Treatment of FXS

Current approaches to therapy are supportive and symptom based. Psychopharmacologic intervention to modify behavioral problems in a child with fragile X syndrome may represent an important adjunctive therapy when combined with other supportive strategies including speech therapy, occupational therapy, special educational services, and behavioral interventions. Medication management may be indicated to modify attention deficits, problems with 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 home and school settings.

Genetics of 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. Diagnosis of FXS may include using a genetic test that determines the number of CGG repeats in the fragile X gene. The patient is classified as normal, intermediate (or “gray zone”), pre-mutation or full mutation based on the number of CGG repeats.
Genetic Testing for FMR1 Mutations Including Fragile X Syndrome

Full mutation: >200-230 CGG repeats (methylated)
Pre-mutation: 55-200 CGG repeats (unmethylated)
Intermediate: 45-54 CGG repeats (unmethylated)
Normal: 5-44 CGG repeats (unmethylated)

Full mutations are associated with FXS, which is caused by 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.

Patients with a premutation are carriers and may develop an FMR1-related disorder, such as fragile X–associated tremor/ataxia syndrome (FXTAS) or, fragile X–associated premature ovarian insufficiency. FXTAS 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.

Pre-mutation alleles in females are unstable and may expand to full mutations in offspring. Pre-mutations of less than 59 repeats have not been reported to expand to a full mutation in a single generation. Pre-mutation alleles in males may expand or contract by several repeats with transmission; however, expansion to full mutations has not been reported.

Pre-mutation allele prevalence in Caucasians is approximately 1 in 1,000 males and 1 in 350 females.

Full mutations are typically maternally transmitted. The mother of a child with an FMR1 variant is almost always a carrier of a pre-mutation or full mutation. Individuals with a pre-mutation are at risk of premature ovarian insufficiency and at small risk of FXTAS; they carry a 50% risk of transmitting an abnormal gene, which either contains a pre-mutation copy number (55-200) or a full mutation (>200) in each pregnancy.

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

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The Xpansion Interpreter® test is available under the auspices of CLIA. The laboratory offering the service 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 these tests.

Asuragen offers the Xpansion Interpreter® test which analyzes AGG sequences that interrupt the CGG repeats which have been suggested to stabilize alleles and protect against expansion in subsequent generations.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing for FMR1 variants when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application
Genetic Testing for FMR1 Mutations Including Fragile X Syndrome

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**When Genetic Testing for FMR1 Mutations is covered**

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

- Individuals of either sex with intellectual disability, developmental delay, or autism spectrum disorder
- Individuals seeking reproductive counseling 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
- Affected individuals or their relatives who have had a positive fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives
- Individuals who have ovarian failure before the age of 40 in whom fragile X-associated ovarian failure is suspected
- Individuals with neurologic symptoms and findings consistent with Fragile X associated tremor and ataxia syndrome

**When Genetic Testing for FMR1 Mutations is not covered**

Genetic testing for FMR1 mutations is considered investigational in the absence of the above clinical indications.

**Policy Guidelines**

Fragile X syndrome is the most common inherited cause of intellectual disabilities and the most common genetic cause of autism. The diagnosis includes use of a genetic test that determines the number of CGG repeats in the fragile X gene, FMR1. FMR1 mutation 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 mutations or positive cytogenetic fragile X testing. The genetics of FXS are complex, and there is a broad spectrum of clinical involvement across generations in families affected by fragile X mutations. A thorough family history, patient assessment, and genetic counseling should guide testing for individuals affected by the many manifestations of these mutations.

The evidence for FMR1 variant testing in individuals with intellectual disability, developmental delay, autism spectrum disorder, who are asymptomatic with a history of fragile X syndrome (FXS) or intellectual disability seeking reproductive counseling, with known FMR1 variant carrier status and current pregnancy seeking prenatal testing, who are asymptomatic with a positive cytogenetic fragile X test result seeking further counseling on carrier status risk, with ovarian failure before age 40 with clinical suspicion of fragile X-associated ovarian failure, or with neurologic symptoms consistent with fragile X-associated tremor/ataxia syndrome who receive FMR1 variant testing, includes studies evaluating the analytic and clinical validity of FMR1 variant testing. Relevant outcomes are test accuracy, and/or resource utilization, and/or changes in reproductive decision making analytic sensitivity and specificity for diagnosing these disorders has been demonstrated to be sufficiently high.
Genetic Testing for FMR1 Mutations Including Fragile X Syndrome

The evidence demonstrates that FMR1 mutation testing can establish a definitive diagnosis of FXS and fragile X-related syndromes when the test is positive for a pathogenic mutation. Following a definitive diagnosis, there are a variety of ways management may change. Providing a diagnosis can eliminate the need for further clinical workup. For certain variants, results may aid in management of psychopharmacologic interventions, assist in informed reproductive decision making, or both. A chain of evidence supports improved outcomes following FMR1 mutation testing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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). The purpose of these recommendations was to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the FMR1:

- “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 first tier testing.

The American Academy of Pediatrics recommends that, because children with FXS may not have apparent physical features, any child who presents with developmental delay, borderline intellectual abilities, or mental retardation, or has a diagnosis of autism without a specific etiology should undergo molecular testing for FXS to determine the number of CGG repeats.

American Congress of Obstetricians and Gynecologists (Committee Opinion, 2017) recommends that prenatal testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation, to individuals with a medical history suggestive of being a fragile X carrier (ie, ovarian insufficiency/failure or an elevated follicle-stimulating hormone level before age 40), and to individuals with a family history of fragile X-related disorders, such as unexplained mental retardation or developmental delay, autism, or premature ovarian insufficiency.

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81171, 81172, 81243, 81244*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.
Genetic Testing for FMR1 Mutations Including Fragile X Syndrome

Scientific Background and Reference Sources


American Congress of Obstetricians and Gynecologists (ACOG). Committee Opinion #469: Carrier Screening for Fragile X Syndrome. [Link to ACOG Committee Opinion]

Medical Director review 7/2012
Specialty Matched Consultant Advisory Panel review 1/2013


Specialty Matched Consultant Advisory Panel review 1/2014
Medical Director review 1/2014


Specialty Matched Consultant Advisory Panel review 4/2015
Medical Director review 4/2015


Medical Director review 3/2016

Medical Director review 1/2017

Specialty Matched Consultant Advisory Panel review 3/2017
Medical Director review 3/2017

Genetic Testing for FMR1 Mutations Including Fragile X Syndrome

Specialty Matched Consultant Advisory Panel review 3/2018
Medical Director review 3/2018

Policy Implementation/Update Information

8/7/12 New policy developed. Genetic testing for FMR1 mutations may be considered medically necessary for the following patient populations: Individuals of either sex with mental retardation, developmental delay, or autism spectrum disorder, Individuals seeking reproductive counseling who have a family history of fragile X syndrome or a family history of undiagnosed mental retardation, Prenatal testing of fetuses of known carrier mothers, 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. Genetic testing for FMR1 mutations is considered investigational in the absence of the above clinical indications. Medical Director review 7/2012. Policy noticed on 8/7/12 for effective date of 11/13/12. (mco)

2/12/13 Specialty Matched Consultant Advisory Panel review 1/2013. No changes to Policy Statements. (mco)

7/30/13 References updated. No changes to Policy Statements. (mco)

2/25/14 Specialty Matched Consultant Advisory Panel review 1/2014. Medical Director review 1/2014. Added the following clinical conditions to the “When Covered” section: “Women who have ovarian failure before the age of 40; Individuals with symptoms consistent with Fragile X associated tremor and ataxia.” (mco)

8/12/14 Policy Guidelines updated. References updated. No changes to Policy Statements. (mco)


7/28/15 References updated. (td)

10/1/15 Description section updated. When Covered section revised. Policy Guidelines section revised. Policy Statements remain unchanged. References updated. (td)


12/30/16 Minor revisions to description and policy guidelines section. No change to policy statement/intent. (jd)

2/24/17 Minor word additions for clarity to “When Covered” section of the Policy Statement but no change to policy intent. Policy Guidelines and references updated. Medical Director review 1/2017. (jd)


Genetic Testing for FMR1 Mutations Including Fragile X Syndrome

12/31/18   Added CPT codes 81171 and 81172 to Billing/Coding section for effective date 1/1/2019.
(jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.