| BLUE CROSS OF NORTHEASTERN PA<br>"BCNEPA"<br>MEDICAL POLICY BULLETIN | **MANUAL:** MEDICAL POLICY |
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| | **REFERENCE NO.:** MPO-083-0038 |
| **EFFECTIVE DATE**<br>October 1, 2014 | **SUBJECT:** Genetic Testing for FMR1 Mutations (Including Fragile X Syndrome) |

**Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy**

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

## DESCRIPTION:

Fragile X syndrome (FXS) is the most common inherited form of mental 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.

## BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins. BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

**BACKGROUND:**

## 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.

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 size of 200 or more repeats.(1) A considerable number of children evaluated for autism have been found to have *FMR1* premutations (55-200 CGG repeats).(2) In one author's experience, 2% of persons ascertained through a dedicated autism clinic had either an *FMR1* full mutation or premutation.

## Treatment of FXS

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 educational 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 home and school settings.

## Genetics of FXS

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"), permutation, or full mutation based on the number of CGG repeats(3):

- Full mutation: >200-230 CGG repeats (methylated)
- Premutation: 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 (FMRP).

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

Premutation alleles 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 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.(3-5) Full mutations are typically maternally transmitted. The mother of a child with an *FMR1* mutation is almost always a carrier of a premutation or full mutation. Women with a premutation are at risk of premature ovarian insufficiency and at small risk of FXTAS; they 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 intellectual disability and decreased fertility.

**MEDICAL POLICY STATEMENT:**

BCNEPA will provide coverage for genetic testing for *FMR1* mutations when medically necessary.

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

- Individuals of either sex with intellectual disability, developmental delay, or autism spectrum disorder (see Policy Guidelines section*).
- Individuals seeking reproductive counseling who have a family history of fragile X syndrome or a family history of undiagnosed intellectual disability (see Policy Guidelines section*).
- Prenatal testing of fetuses of known carrier mothers (see Policy Guidelines section*).
- 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 (see Policy Guidelines section**).

Genetic testing for *FMR1* mutations is considered not medically necessary for all other uses.

**GUIDELINES:**

* According to the American College of Medical Genetics (ACMG), the following is the preferred approach to testing:

- DNA analysis is the method of choice if one is testing specifically for fragile X syndrome and associated trinucleotide repeat expansion in the *FMR1* gene.
- For isolated cognitive impairment, DNA analysis for fragile X syndrome should be performed as part of a comprehensive genetic evaluation that includes routine cytogenetic evaluation. Cytogenetic evaluation is important in these circumstances because constitutional chromosome abnormalities have been identified as frequently as or more frequently than fragile X mutations in mentally retarded patients referred for fragile X testing.

- Fragile X testing is not routinely warranted for children with isolated attention-deficit/hyperactivity.(8)
- 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 1 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 chorionic villus sampling at 10 to 12 weeks' gestation, but 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. 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 before 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.

** This is due to the fact that cytogenetic testing was used before the identification of the *FMR1* gene and is significantly less accurate than the current DNA test. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women.(9)

The ACMG Professional Practice and Guidelines Committee made recommendations regarding diagnostic and carrier testing for fragile X syndrome to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the *FMR1* gene. These recommendations include testing of individuals of either sex who have intellectual disability, developmental delay, or autism, especially if they have any physical or behavioral characteristics of fragile X syndrome.(9)

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 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.

**RATIONALE:**

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disabilities and the most common genetic cause of autism. 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. Analytic sensitivity and specificity for diagnosing these disorders has been demonstrated to be sufficiently high.

There are a variety of ways management may change as a result of genetic testing. Evidence on the impact on health outcomes of documenting *FMR1* gene mutations is largely anecdotal but may end the need for additional testing in the etiologic workup of an intellectual disability, aid in management of

psychopharmacologic interventions, and assist in reproductive decision making. Therefore, genetic testing for *FMR1* mutations may be considered medically necessary in individuals of either sex with intellectual disability, developmental delay, or autism spectrum disorder, and for other clinical scenarios outlined in the policy statements.

**Practice Guidelines and Position Statements**

American College of Medical Genetics

ACMG's Professional Practice and Guidelines Committee makes the following recommendations regarding diagnostic and carrier testing for FXS.(9) The purpose of these recommendations is to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the *FMR1* gene.

- Individuals of either sex with intellectual disability, developmental delay, or autism, especially if they have (a) any physical or behavioral characteristics of fragile X syndrome, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed intellectual disability.
- Individuals seeking reproductive counseling who have (a) a family history of fragile X syndrome or (b) a family history of undiagnosed intellectual disability.
- Fetuses of known carrier mothers.
- Affected individuals or their relatives in the context of a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. The cytogenetic test was used 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 recommends testing for FXS as part of first tier testing.(1)

Academy of Pediatrics

AAP recommends that, because children with FXS may not have apparent physical features, any child who presents with developmental delay, borderline intellectual abilities, or intellectual disability, or has a diagnosis of autism without a specific etiology should undergo molecular testing for FXS to determine the number of CGG repeats.(5)

American Congress of Obstetricians and Gynecologists

ACOG (Committee Opinion, 2010) recommends that prenatal testing for FXS should be offered to known carriers of the fragile X premutation or full mutation, and to women with a family history of fragile X-related disorders, unexplained intellectual disability or developmental delay, autism, or premature ovarian insufficiency.(18)

**DEFINITIONS:**

N/A

**CODING:**



- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

**PROCEDURE CODES**

81243 81244

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**APPROVALS:**

Approved by Vice President, Clinical Operations & Chief Medical Officer:

Signature:_____
(Nina M. Taggart, MA, MD, MBA)

Date of Approval: September 17, 2014

**HISTORY:**

Original Development Date: (10/01/14)

Policy developed by: Medical Policy Department