The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is required. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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.

Background

Fragile X syndrome

Fragile X syndrome (FXS) is the most common cause of heritable mental retardation, characterized by moderate mental retardation in males and mild mental retardation 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 premutations (55-200 CGG repeats). (1) In one author’s experience, 2% of persons ascertained through a dedicated autism clinic had either an FMR1 full mutation or premutation.

Treatment of fragile X syndrome

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 one (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”), premutation or full mutation based on the number of CGG repeats.

Patients with a full mutation are associated with FXS, which is caused by expansion of the FMR1 gene CGG triplet repeat above 200 units in the 50 untranslated region of FMR1, leading to a hypermethylation of the promoter region followed by transcriptional inactivation of the gene. The FXS is caused by a loss of the fragile X mental retardation protein (FMRP).

Those with a premutation are carriers and may have a FMR1-related disorder: fragile X-associated tremor/ataxia syndrome (FXTAS), which is a late onset, 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 or premature ovarian insufficiency (POI).

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)

Premutation alleles in females are unstable and may expand to full mutations in offspring. Premutations of less 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 Caucasians is one in 1,000 males and one in 350 females. 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 either contains 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 mental retardation and decreased fertility.

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

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.

Corporate Medical Guideline

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 (see Policy Guidelines*).
• Individuals seeking reproductive counseling who have a family history of fragile X syndrome or a family history of undiagnosed mental retardation (see Policy Guidelines*).
• Prenatal testing of fetuses of known carrier mothers (see Policy Guidelines*).
• 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 (see Policy Guidelines**).

Genetic testing for FMR1 mutations is considered investigational in all other patient populations.

Policy Guideline

*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 since constitutional chromosome abnormalities have been identified as frequently 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.
• 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.

**This is due to the fact that cytogenetic testing was used prior to 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.

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 with mental retardation, developmental delay, or autism, especially if they have any physical or behavioral characteristics of fragile X syndrome.
Physical and behavioral characteristics of fragile X syndrome include: 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.