Medical Coverage Policy

Genetic Testing: Rett Syndrome - PREAUTH

- Device/Equipment
- Drug
- Medical
- Surgery
- Test
- Other

Effective Date: 12/18/2012
Policy Last Updated: 12/18/2012

☑ Prospective review is recommended/required. Please check the member agreement for preauthorization guidelines.

☐ Prospective review is not required.

Description:
Fragile X syndrome is the most common cause of inheritable mental retardation and is characterized by moderate mental retardation in males and mild mental retardation in females. Fragile X syndrome 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.

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.

Fragile X syndrome 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 fragile X syndrome may include the use of 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 fragile X syndrome, 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 fragile X syndrome 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 1 in 1,000 males and 1 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.

Fragile X syndrome is the most common inherited cause of intellectual disabilities and the most common genetic cause of autism. The genetics of fragile X syndrome are complex, and there is a broad spectrum of clinical involvement throughout the generations of families affected by the 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 mental retardation, developmental delay, or autism spectrum disorder, and for the other clinical scenarios as outlined in the policy statements.

**Medical Criteria:**

Genetic testing for FMR1 mutations may be considered **medically necessary** for individuals of either sex with mental retardation, developmental delay, or autism spectrum disorder.

Genetic testing for FMR1 mutations is considered screening and a **contract exclusion** for:

- 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; **OR**
- 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.

**Policy:**

Genetic testing for FMR1 mutations is covered when the medical criteria above has been met.
Prior authorization is required for BlueCHiP for Medicare and recommended for all other BCBSRI products.

**Coverage:**
Benefits may vary between groups and contracts. Please refer to the appropriate Evidence of Coverage, Subscriber Agreement, or Benefit Booklet for applicable benefits/coverage.

**Coding:**
81243
81244

**Also known as:**
Not applicable

**Related topics:**
Array Comparative Genomic Hybridization (aCGH) for the Genetic Evaluation of Patients with Developmental Delay/Mental Retardation or Autism Spectrum Disorder

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**References:**


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