GUIDELINES

This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder contract. Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. This guideline is solely for explaining correct procedure reporting and does not imply coverage and reimbursement.

DESCRIPTION

Fragile X syndrome (FMR1 Gene) is the most common cause of heritable intellectual disability, characterized by moderate intellectual disability in males and mild intellectual disability 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, velvety-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.)

Fragile X syndrome takes its name from the appearance of the stained X chromosome under a microscope. There is a site near the end of this chromosome that does not stain, indicating its fragility. (Note: This methodology is no longer used for Fragile X testing). The gene in the fragile region is important in making a special protein needed by developing brain cells. DNA-based molecular analysis (eg, Southern blot analysis and polymerase chain reaction) is the preferred method of diagnosis of Fragile X syndrome and of determining FMR1 triplet repeat number (eg, premutation/mutation status).

Outside of Fragile X syndrome, individuals who have premutations are at an increased risk for Fragile X-related primary ovarian insufficiency as well as Fragile X-related tremor/ataxia syndrome. Women with Fragile X-related primary ovarian insufficiency may experience irregular menstrual cycles, infertility, and early menopause. Individuals who have Fragile X-related tremor/ataxia syndrome can experience ataxia (progressive issues with movement), tremors, memory loss, peripheral neuropathy as well as mental/behavioral issues.

POLICY

Fragile X-related Disorders (FMR1 Gene) genetic testing (81243, 81244) requires prior authorization for HMO, PPO, Individual Marketplace, & Advantage.

Fragile X-related Disorders (FMR1 Gene) genetic testing (81243, 81244) is non-covered for Elite.

HMO, PPO, Individual Marketplace, Advantage

Paramount covers Fragile X-related Disorders (FMR1 Gene) genetic testing when any of the following criteria are met:

- Individual to be tested has intellectual disability, developmental delay or autism spectrum disorder (ASD)
- Individual to be tested exhibits clinical features of Fragile X syndrome (eg, macrocephaly, large ears, enlarged testes, perseverative speech and poor eye contact)
- Individual to be tested diagnosed with unexplained POI (also known as premature ovarian failure) which is defined as individuals younger than 40 years with irregular menses in association with elevated FSH levels.
- Individual with family history of Fragile X-related disorders or unexplained mental retardation, developmental disorder and/or autism spectrum disorder who is considering pregnancy or currently pregnant
- Testing of fetus if mother is a known carrier of Fragile X (permutation or full mutation)
- Individual to be tested is at least 50 years old with cerebellar ataxia of unknown origin
- Individual to be tested is at least 50 years old with onset of action tremor of unknown case with parkinsonism or cognitive decline
- Individual to be tested has a prior diagnosis of multiple system atrophy, cerebellar subtype
- Individual to be tested has MCP sign on T2/FLAIR images of MRI and has features consistent with Fragile-X Associated Tremor/Ataxia syndrome (e.g. action tremor, cerebellar gait ataxia, parkinsonism, cognitive decline, executive function deficits)

**Elite**

Fragile X syndrome (*FMR1* Gene) genetic testing is non-covered per CMS guidelines.

**CODING/BILLING INFORMATION**

The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

<table>
<thead>
<tr>
<th>CPT CODE</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>81243</td>
<td><em>FMR1</em> (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles</td>
</tr>
<tr>
<td>81244</td>
<td><em>FMR1</em> (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status)</td>
</tr>
</tbody>
</table>

**TAWG REVIEW DATES:** 04/22/2016, 02/22/2018

**REVISION HISTORY EXPLANATION**

04/22/16: Policy created to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

11/23/16: Gender verbiage changes completed per Meaningful Access Section 1557 of the Affordable Care Act.

11/14/17: Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

02/22/18: Added coverage criteria: Individual with family history of Fragile X-related disorders or unexplained mental retardation, developmental disorder and/or autism spectrum disorder who is considering pregnancy or currently pregnant, & Testing of fetus if mother is a known carrier of Fragile X (permutation or full mutation). Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

07/09/19: Changed title to Fragile X-Related Disorders. Clarified information in the description section. Added information regarding Fragile X-related POI and tremor/ataxia syndrome. Added criteria for testing related to ataxia/tremors from the Movement Disorder Society. Added references.

**REFERENCES/RESOURCES**

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services
Ohio Department of Medicaid [http://jfs.ohio.gov/](http://jfs.ohio.gov/)
Industry Standard Review
Hayes, Inc.
National Institute of Health, Genetics Home Reference, Fragile X syndrome, April 2019
American College of Obstetricians and Gynecologists (ACOG), Carrier Screening for Fragile X syndrome, Committee Opinion No. 469
Genetic Counseling for Fragile X Syndrome: Updated Recommendations of the National Society of Genetic Counselors (NSGC), 2005
American College of Medical Genetics and Genomics (ACMG), Fragile X syndrome: Diagnostic and carrier testing, 2005
ACMG Standards and Guidelines for Fragile X Testing: A Revision to the Disease-Specific Supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the ACMG, 2013
Movement Disorder Society, Fragile X-Associated Tremor/Ataxia Syndrome: Clinical Features, Genetics, and Testing Guidelines