Fragile X Associated Tremor/Ataxia Syndrome Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMR1 Expansion Analysis</td>
<td>81243</td>
</tr>
</tbody>
</table>

What is fragile X-associated tremor/ataxia syndrome

Definition

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder characterized by progressive cerebellar ataxia and/or intention tremor usually presenting after age 50 in individuals with a premutation allele in the gene for fragile X (FMR1).¹

- Fragile X syndrome, FXTAS, and other related disorders are caused by a type of genetic mutation called a triplet repeat. A triplet repeat is a sequence of three nucleotide building blocks (CGG) that is variably repeated within the FMR1 gene. The number of triplet repeats determines whether the gene is normal, intermediate, or has a premutation or full mutation.³,⁴ Premutation carriers — the group at risk for FXTAS — have 55 to 200 CGG repeats.¹
- Both male and female premutation carriers are at risk for FXTAS. Approximately 40% of males over the age of 50, with a premutation allele, will develop FXTAS. The risk to female premutation carriers appears to be lower.¹,²
- Other neurologic findings of FXTAS include:¹
  - Short term memory loss
  - Executive function deficits
  - Cognitive decline
  - Dementia
  - Parkinsonism
  - Peripheral neuropathy
  - Lower limb proximal weakness
• A diagnosis is confirmed by the presence of a FMR1 premutation and white matter lesions on MRI in the middle cerebellar peduncles and/or brain stem, with intention tremor and/or gait ataxia.¹

Test information
• FMR1 CGG expansion analysis measures the number of CGG repeat copies within the FMR1 gene. Repeat number classifies results as normal, intermediate, premutation, or full mutation.²³ The same analysis can be used for diagnostic, carrier, and prenatal testing.

Guidelines and evidence
• Consensus guidelines from the American College of Medical Genetics (ACMG, 2005) recommend FXTAS testing for the following people:
  o “Men and women who are experiencing late onset intention tremor and cerebellar ataxia of unknown origin, especially if they have (a) a family history of movement disorders, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation.” ³
• Evidence-based guidelines from the European Federation of Neurological Societies (EFNS, 2010) state:
  o “Recommendations for FXTAS genetic testing: Genetic testing for the X-linked FXTAS is recommended when there is a clinical suspicion, and it is readily available in many laboratories (Class B).” ⁴ [Class B rating = “(probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence” ⁵]

Criteria
Targeted mutation analysis for CGG trinucleotide repeat expansion in FMR1
• Genetic Counseling:
  o Medical evaluation by a physician familiar with FXTAS, and
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous molecular genetic testing of FMR1, AND
• Diagnostic Testing for Symptomatic Individuals:
• Prenatal Testing for At-Risk Pregnancies
  o CGG trinucleotide repeat expansion in FMR1 identified in biological mother,**
    OR
• Carrier Screening and Predictive Testing for Presymptomatic/Asymptomatic At Risk
  Individuals:
  o Known CGG trinucleotide repeat expansion in FMR1 in 1st, 2nd, or 3rd degree
    biologic relative, or
  o Personal or family history of premature ovarian failure (cessation of menses
    before age of 40 years), or
  o Family history of movement disorder, and
    ▪ Cerebellar ataxia has been ruled out, and
    ▪ Other movement disorders have been ruled out, or
  o Family history of intellectual disability with an unknown cause, or
  o Prior cytogenetic test suspicious for Fragile X, and
  o Age 18 years or older
  o Intellectual disability, AND
• Possibility of X-linked inheritance has not been ruled out by male to male
  transmission

** Note: CVS must be interpreted with caution. The number of CGG repeats in the
fetus can be accurately determined; however, often the methylation status of FMR1 is
not yet established in chorionic villi at the time of sampling. CVS results may lead to a
situation in which follow-up amniocentesis is necessary to resolve an ambiguous result.

References
1. Saul R, Tarleton J. FMR1-Related Disorders. (Updated April 2012). In: GeneReviews at
   GeneTests: Medical Genetics Information Resource (database online). Copyright, University of
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   counseling for fragile X syndrome: updated recommendations of the national society of genetic
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