



**GENETIC TESTING FOR FRAGILE X SYNDROME AND
OTHER FMR1 GENE-RELATED CONDITIONS
HS-123**



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Harmony Behavioral Health of Florida, Inc.

Harmony Health Plan of Illinois, Inc.

HealthEase of Florida, Inc.

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**Genetic Testing for Fragile X
Syndrome and Other FMR1
Gene-Related Conditions**

Policy Number: HS-123

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DISCLAIMER

The Clinical Coverage Guideline is intended to supplement certain standard WellCare benefit plans. The terms of a member's particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member's benefit plan may contain specific exclusions related to the topic addressed in this Clinical Coverage Guideline. When a conflict exists between the two documents, the Member's Benefit Plan always supersedes the information contained in the Clinical Coverage Guideline. Additionally, Clinical Coverage Guidelines relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

BACKGROUND

Fragile X syndrome is the most common cause of inherited mental retardation and is due to a mutation in the X-linked FMR1 gene. Males with fragile X syndrome almost always exhibit mental retardation, usually in the moderate range, and often have characteristic physical features and behavior. Since the mutation is X-linked, males are more severely affected than females. Thus, affected females tend to have mild mental retardation, and have variable associated physical features.

The mutation leading to over 98% of cases of fragile X syndrome is an expansion of an unstable CGG repeat sequence located in the 5' untranslated region (UTR) of the FMR1 gene. There are essentially four allelic forms of the gene with respect to repeat length. They are referred to as common, "gray zone" or intermediate, premutation, and full mutation. The associated repeat sizes for each group are not well-defined and, as such, complicate genetic counseling. The full mutation form of the FMR1 gene consists of over 200 repeats and is abnormally hypermethylated. Consequently, the gene is silenced and no mRNA is produced. The lack of the gene product, FMRP, an RNA-binding protein, is responsible for the mental retardation.

The clinical consequences of the expanded CGG repeat in the FMR1 gene were thought to be restricted to those with the full mutation (hence the term "full"), namely, overt mental retardation. However, the unmethylated, long CGG repeat track found in premutation carriers has been associated with specific phenotypes unrelated to fragile X syndrome and unrelated to full mutation carriers. One well recognized consequence for women who carry the premutation allele is an increased risk for premature ovarian failure (POF), clinically defined as the cessation of menses before the age of 40. Among women who carry the premutation, approximately 21% have POF compared to only 1% in the general population, or a relative risk of 21. Furthermore, approximately 2% and 14% of women with isolated POF and familial POF, respectively, carry the premutation allele. This high carrier frequency compares with 0.3% in the general population.

More recently, a significant increase in the risk for a late onset neurodegenerative disorder with tremor/ataxia syndrome (FXTAS) has been identified in men who carry the premutation, and in a smaller proportion of women. The primary clinical symptoms are cerebellar ataxia and intention tremor. Other documented symptoms include cognitive deficits such as short-term memory loss, executive function deficits, cognitive decline, parkinsonism, peripheral neuropathy, lower limb proximal muscle weakness and autonomic dysfunction. Initial studies indicate a penetrance of combined tremor and ataxia among men ages 50 years or more with the premutation of about 20–40% (ACMG, 2005).

POSITION STATEMENT

Genetic testing of the repeat region of the FMR1 gene **is considered medically necessary** in the following circumstances:

1. Fragile X Syndrome

- a. Members of either sex with mental retardation with unknown etiology (or mental retardation cannot be excluded), developmental delay*, or autism, with **ANY** of the following:
 - Any physical or behavioral characteristics of fragile X syndrome; **OR**,
 - **V18.9** A family history of fragile X syndrome; **OR**,
 - **V18.4** Male or female history of undiagnosed mental retardation
- b. Members seeking reproductive counseling who have **ANY** of the following:
 - **V18.9** A family history of fragile X syndrome; **OR**,
 - **V18.4** A family history of undiagnosed mental retardation

- c. **V18.9** Fetuses of known carrier mothers
- d. **V26.33** Affected members in the context of a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status*

***NOTE: 783.40 Developmental delay is defined using the following criteria:**

- No babbling by 12 months; **OR**,
- No gesturing (e.g., pointing, waving bye) by 12 months; **OR**,
- No single words by 16 months; **OR**,
- No two-word spontaneous (not echolalic) phrases by 24 months; **OR**,
- None-to-little mutual gaze or joint attention

**NOTE: The cytogenetic test was used prior to 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 permutation carriers and to distinguish permutation from full mutation carrier women.

2. Ovarian Dysfunction

- a. **256.9** Women who are experiencing reproductive or fertility problems associated with elevated follicle stimulating hormone (FSH) levels with **ANY** of the following:
- V18.7 A family history of premature ovarian failure; **OR**,
 - V18.9 A family history of fragile X syndrome; **OR**,
 - V18.4 Male or female relatives with undiagnosed mental retardation

3. Tremor/Ataxia Syndrome

- a. **334.8** Men and women who are experiencing late onset intention tremor and cerebellar ataxia of unknown origin with **ANY** of the following:
- V17.89 A family history of movement disorders; **OR**,
 - V18.9 A family history of fragile X syndrome; **OR**,
 - V18.4 Male or female relatives with undiagnosed mental retardation

General population carrier screening of the repeat region of the FMR1 gene is **considered NOT medically necessary**.

CODING

Covered CPT® Codes

88248 Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangiectasia, Fanconi anemia, **Fragile X**),

ICD-9-CM Procedure Codes - No applicable codes

HCPCS Codes - No applicable codes

Covered ICD-9-CM Diagnosis Codes

256.8 – 256.9	Ovarian Dysfunction
344.3	Cerebellar Ataxia
V17.2	Family history of other neurological diseases
V17.89	Family history of musculoskeletal diseases
V18.4	Family history of mental retardation
V18.9	Family history of genetic disease carrier, i.e. Fragile X
V26.33	Genetic counseling
V80.0	Special screening for neurological conditions
V83.89	Other genetic carrier status
V84.89	Genetic susceptibility to other disease

Non Covered ICD-9-CM Diagnosis Codes

General population carrier screening of the repeat region of the FMR1 gene is considered NOT medically necessary.

V26.31	Testing of female for genetic disease carrier status
V26.34	Testing of male for genetic disease carrier status

*Current Procedural Terminology (CPT) 2010 American Medical Medical Association: Chicago, IL.

REFERENCES

Peer Reviewed

1. Hayes, Inc GTE Report. Fragile X Syndrome (FMR1). August 7, 2008.

Government Agencies, Professional and Medical Organizations

1. American College of Medical Genetics. Fragile X Syndrome: Diagnostic and carrier testing. Sherman, et al. ACMG Practice Guideline, Vol. 7, No. 8, October, 2005.
2. American College of Medical Genetics. Technical 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 American College of Medical Genetics. Standards and Guidelines for Clinical Genetics Laboratories, 2006 Edition.

HISTORY AND REVISIONS

Date	Action
12/1/2011	• New template design approved by MPC.
8/2/2011	• Approved by MPC. No changes.