Easy Choice Health Plan, Inc.
Harmony Health Plan of Illinois, Inc.
Missouri Care, Inc.
‘Ohana Health Plan, a plan offered by WellCare Health Insurance of Arizona, Inc.
WellCare Health Insurance of Illinois, Inc.
WellCare Health Plans of New Jersey, Inc.
WellCare Health Insurance of Arizona, Inc.
WellCare of Florida, Inc.
WellCare of Connecticut, Inc.
WellCare of Georgia, Inc.
WellCare of Kentucky, Inc.
WellCare of Louisiana, Inc.
WellCare of New York, Inc.
WellCare of Ohio, Inc.
WellCare of South Carolina, Inc.
WellCare of Texas, Inc.
WellCare Prescription Insurance, Inc.
Windsor Health Plan
Windsor Rx Medicare Prescription Drug Plan

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

Policy Number: HS-123

Original Effective Date: 8/20/2009

Revised Date(s): 8/20/2010; 8/2/2011;
8/2/2012; 8/1/2013; 8/7/2014

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.
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. Note: The lines of business (LOB) are subject to change without notice; consult www.wellcare.com/Providers/CCGs for list of current LOBs.

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.1

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, pre-mutation, 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.1

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 pre-mutation 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 pre-mutation 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 pre-mutation, 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 pre-mutation allele. This high carrier frequency compares with 0.3% in the general population.1

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 pre-mutation, 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 pre-mutation of about 20–40%.2

POSITION STATEMENT

Applicable To:

☑ Medicaid – Hawaii, Kentucky*
☑ Medicare – Easy Choice Health Plan, Hawaii, Kentucky*

For markets noted below, please refer to Care Core National Lab Management criteria (program effective August 2014) available at www.wellcare.com/provider/CCGs.

☑ Medicaid – Florida, Georgia, Illinois, Missouri, New Jersey, New York, South Carolina

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Original Effective Date: 8/20/2009 - Revised: 8/20/2010, 8/2/2011, 8/2/2012, 8/1/2013, 8/7/2014
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.

Testing for Fragile X Syndrome is a covered benefit for the following indications:
   - For predictive testing for CGG repeat length to determine the carrier status of asymptomatic individuals with a family history of fragile X syndrome or a family history of undiagnosed mental retardation, and to define risk of transmission.
   - For prenatal testing for CGG repeat length in fetuses from families in which there is a family history of fragile X syndrome.
   - For preimplantation testing for CGG repeat length in embryos from carrier mothers with a known premutation in the FMR1 gene.
   - For testing for CGG repeat length for diagnosis of patients of either sex with mental retardation, developmental delay, or autism.

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
81243 FMR1 (Fragile X mental retardation 1) (e.g. fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g. expanded) alleles (this CPT code effective 01/01/2012)
81244 FMR1 (Fragile X mental retardation 1) (e.g. fragile X mental retardation) gene analysis; characterization of alleles (e.g. expanded size and methylation status) (effective 01/01/2012)
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)

HCPCS Codes - No applicable codes

ICD-9-CM Procedure Codes - No applicable codes

DRAFT 2013 ICD-10-PCS Codes – No applicable codes

Covered ICD-9-CM Diagnosis Codes
256.8 - 256.9 Ovarian Dysfunction
334.3 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
V80.09 Special screening for neurological conditions Type should be V80.09
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

Covered Draft 2013 ICD-10-CM Diagnosis Codes
E28.8 Other ovarian dysfunction
E28.9 Other ovarian dysfunction, unspecified
GENETIC TESTING FOR FRAGILE X SYNDROME AND OTHER FMR1 GENE-RELATED CONDITIONS

HS-123

G11.1  Early onset cerebellar ataxia
Z13.858  Encounter for screening for other nervous system disorders
Z14.8  Genetic carrier of other disease
Z15.89  Genetic susceptibility to other disease
Z31.5  Encounter for genetic counseling
Z81.0  Family history of mental retardation
Z82.0  Family history of epilepsy and other diseases of the nervous system
Z82.69  Family history of other diseases of the musculoskeletal system and connective tissue
Z84.81  Family history of carrier of genetic disease

Non-covered  Draft 2013 ICD-10-CM Diagnosis Codes
General population carrier screening of the repeat region of the FMR1 gene is considered NOT medically necessary
Z31.430  Encounter of female for testing for genetic disease carrier status for procreative management
Z31.440  Encounter of male for testing for genetic disease carrier status for procreative management


REFERENCES

MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

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<tr>
<td>8/7/2014</td>
<td>Approved by MPC. Clarified lines of business. No changes to coverage.</td>
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<td>8/1/2013</td>
<td>Approved by MPC. No changes.</td>
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<tr>
<td>8/2/2012</td>
<td>Approved by MPC. No changes.</td>
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<tr>
<td>12/1/2011</td>
<td>New template design approved by MPC.</td>
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