2.04.83 Genetic Testing for FMR1 Mutations (Including Fragile X Syndrome)

Summary

Fragile X syndrome (FXS) is the most common inherited form of mental disability and known genetic cause of autism. The diagnosis includes use of a genetic test that determines the number of CGG repeats in the fragile X gene, FMR1. FMR1 mutation testing has been investigated in a variety of clinical settings, including in the evaluation of individuals with a personal or family history of intellectual disability, developmental delay, or autism spectrum disorder and in reproductive decision-making in individuals with known FMR1 mutations or positive cytogenetic fragile X testing. The genetics of FXS are complex, and there is a broad spectrum of clinical involvement across generations in families affected by 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.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Genotyping tests for FMR1 mutations are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

POLICY STATEMENT

Genetic testing for FMR1 mutations may be considered medically necessary for the following patient populations:

- Individuals of either sex with intellectual disability, developmental delay, or autism spectrum disorder (see Policy Guidelines section*).
- Individuals seeking reproductive counseling who have a family history of fragile X syndrome or a family history of undiagnosed intellectual disability (see Policy Guidelines section*).
- Prenatal testing of fetuses of known carrier mothers (see Policy Guidelines section*).
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- Affected individuals or relatives of affected individuals who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status (see Policy Guidelines section**).

Genetic testing for FMR1 mutations is investigational for all other uses.

POLICY GUIDELINES (IF NEEDED)

American College of Medical Genetics Recommendations*
According to the American College of Medical Genetics (ACMG) Recommendations, the following is the preferred approach to testing:

- DNA analysis is the method of choice if one is testing specifically for fragile X syndrome and associated trinucleotide repeat expansion in the FMR1 gene.

- For isolated cognitive impairment, DNA analysis for fragile X syndrome should be performed as part of a comprehensive genetic evaluation that includes routine cytogenetic evaluation. Cytogenetic evaluation is important in these circumstances because constitutional chromosome abnormalities have been identified as frequently as or more frequently than fragile X mutations in mentally retarded patients referred for fragile X testing.

- Fragile X testing is not routinely warranted for children with isolated attention-deficit/hyperactivity. (see Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, 2011).

- For individuals who are at risk due to an established family history of fragile X syndrome, DNA testing alone is sufficient. If the diagnosis of the affected relative was based on previous cytogenetic testing for fragile X syndrome, at least 1 affected relative should have DNA testing.

- Prenatal testing of a fetus should be offered when the mother is a known carrier to determine whether the fetus inherited the normal or mutant FMR1 gene. Ideally DNA testing should be performed on cultured amniocytes obtained by amniocentesis after 15 weeks of gestation. DNA testing can be performed on chorionic villi obtained by chorionic villus sampling at 10 to 12 weeks of gestation, but results must be interpreted with caution because the methylation status of the FMR1 gene is often not yet established in chorionic villi at the time of sampling. Follow-up amniocentesis may be necessary to resolve an ambiguous result.

- If a woman has ovarian failure before the age of 40, DNA testing for premutation size alleles should be considered as part of an infertility evaluation and before in vitro fertilization.

- If a patient has cerebellar ataxia and intentional tremor, DNA testing for premutation size alleles, especially among men, should be considered as part of the diagnostic evaluation.

The ACMG Professional Practice and Guidelines Committee made recommendations regarding diagnostic and carrier testing for FXS to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the FMR1 gene. These recommendations include testing of individuals of either sex who have intellectual disability, developmental delay, or autism, especially if they have any physical or behavioral characteristics of fragile X syndrome (see Sherman et al, 2005).

Physical and behavioral characteristics of FXS include: typical facial features, such as an elongated face with 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.
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Cytogenetic Testing
Cytogenetic testing was used before the identification of the FMR1 gene and is significantly less accurate than the current DNA test. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women (see Sherman et al, 2005).

Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

RATIONALE

Summary of Evidence
The evidence for FMR1 mutation testing in individuals with intellectual disability, developmental delay, or autism spectrum disorder or in affected individuals or at-risk relatives in whom testing will affect reproductive decision making includes studies evaluating the analytic and clinical validity of FMR1 mutation testing and a chain of indirect evidence for demonstration of clinical outcome improvements. Relevant outcomes are test accuracy, test validity, resource utilization, and changes in reproductive decision making. Analytic sensitivity and specificity for diagnosing these disorders has been demonstrated to be sufficiently high. The evidence demonstrates that FMR1 mutation testing can establish a definitive diagnosis of FXS when the test is positive for a pathogenic mutation. Following a definitive diagnosis, there are a variety of ways management may change. Providing a diagnosis can eliminate the need for further clinical workup. For certain mutations, results may aid in management of psychopharmacologic interventions, assist in informed reproductive decision making, or both. Although direct evidence for improved outcomes is insufficient, there is a chain of indirect evidence that supports improvements in outcomes following FMR1 mutation testing. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Medical Genetics
American College of Medical Genetics’s (ACMG) Professional Practice and Guidelines Committee makes the following recommendations regarding diagnostic and carrier testing for FXS. The purpose of these recommendations is to provide general guidelines to aid clinicians in making referrals for testing the repeat region of the FMR1 gene.
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- Individuals of either sex with intellectual disability, developmental delay, or autism, especially if they have (a) any physical or behavioral characteristics of fragile X syndrome, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed intellectual disability.
- Individuals seeking reproductive counseling who have (a) a family history of fragile X syndrome or (b) a family history of undiagnosed intellectual disability.
- Fetuses of known carrier mothers.
- Affected individuals or their relatives in the context of a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. The cytogenetic test was used before 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 premutation carriers and to distinguish premutation from full mutation carrier women.

In the clinical genetics evaluation to identify the etiology of autism spectrum disorders, ACMG recommends testing for FXS as part of first tier testing.

Academy of Pediatrics
The Academy of Pediatrics recommends that, because children with FXS may not have apparent physical features, any child who presents with developmental delay, borderline intellectual abilities, or intellectual disability, or has a diagnosis of autism without a specific etiology should undergo molecular testing for FXS to determine the number of CGG repeats.

American Congress of Obstetricians and Gynecologists
The American Congress of Obstetricians and Gynecologists (Committee Opinion, 2010) recommends that prenatal testing for FXS should be offered to known carriers of the fragile X premutation or full mutation, and to women with a family history of fragile X‒related disorders, unexplained intellectual disability or developmental delay, autism, or premature ovarian insufficiency.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

POLICY HISTORY

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<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>September 2013</td>
<td>New Policy</td>
<td>Policy updated with literature review; references 3-4, 6-8, 10-15, and 17-18, added. Policy statements and entire policy updated to reflect current DSM-V diagnostic categories, ie, “intellectual disability” replaces “mental retardation” No change to policy statements except the addition of Genetic testing for FMR1 is investigational for all other uses.</td>
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<tr>
<td>December 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 16 and 20 added. Policy statements unchanged.</td>
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<tr>
<td>September 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 16 and 20 added. Policy statements unchanged.</td>
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<tr>
<td>December 2016</td>
<td>Update Policy</td>
<td>Policy statement unchanged</td>
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Deborah M. Smith, MD, MPH