MEDICAL POLICY

POLICY TITLE	**GENETIC TESTING FOR PATHOGENIC FMR1 VARIANTS (INCLUDING FRAGILE X SYNDROME)**
POLICY NUMBER	**MP 2.276**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**4/1/2025**

I. POLICY

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

- Individuals with characteristics of fragile X syndrome or a fragile X-associated disorder, including:
  - Individuals with intellectual disability, developmental delay, or autism spectrum disorder;
  - Women with primary ovarian insufficiency under the age of 40 in whom fragile X-associated primary ovarian insufficiency is suspected;
  - Individuals with neurologic symptoms consistent with fragile X-associated tremor or ataxia syndrome.
- Individuals who have a personal or family history of fragile X syndrome who are seeking reproductive counseling, including:
  - Individuals who have a family history of fragile X syndrome or a family history of undiagnosed intellectual disability;
  - Affected individuals or relatives of affected individuals who have had a positive cytogenetic fragile X test result who are seeking information on carrier status;
  - Prenatal testing of fetuses of known carrier mothers.

Genetic testing for *FMR1* variants is **investigational** for all other uses as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

Physical and behavioral characteristics of fragile X syndrome include typical facial features, 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,

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 disorder, 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.

Testing Strategy
Detection of CGG triplet repeats in the *FMR1* gene can occur sequentially or in parallel with determination of methylation status:

- In sequential testing, detection of CGG triplet repeats in *FMR1* is performed first. If a large number of repeats (e.g., >55) is detected, reflex methylation testing can be performed to determine methylation status
- In parallel testing, detection methods such as methylation-specific polymerase chain reaction allow for detection of both the size of CGG triplet repeats in *FMR1* and methylation status.

Cytogenic Testing
Cytogenetic testing was used before the identification of the *FMR1* gene and is significantly less accurate than the current DNA test. The method is no longer considered an acceptable diagnostic method according to American College of Medical Genetics and Genomics (ACMG) standards (see Spector et al, 2021).

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.

Cross-Reference:
MP 2.242 Genetic Testing for Developmental Delay-Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies
MP 2.262 Genetic Testing for Epilepsy
MP 2.304 Autism Spectrum Disorders

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II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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Fragile X Syndrome

Fragile X syndrome (FXS) is the most common inherited form of mental disability and a known genetic cause of autism. The diagnosis is made with a genetic test that determines the number of CGG repeats in the fragile X mental retardation 1 gene, (FMR1). FMR1 variant testing has been investigated in a variety of clinical settings, including 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 variants or positive cytogenetic fragile X testing. FMR1 variants also cause premature ovarian failure and a neurologic disease called fragile X-associated ataxia or tremor syndrome.

Fragile X syndrome (FXS) is the most common cause of heritable intellectual disability, characterized by moderate intellectual disability in males and mild intellectual disability in females. FXS affects approximately 1 in 4000 males and 1 in 8000 females. In addition to intellectual impairment, patients present with 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.

Fragile X syndrome (FXS) is associated with the expansion of the CGG trinucleotide repeat in the fragile X mental retardation 1 (*FMR1)* gene on the X chromosome. FXS is associated with the expansion of the *FMR1* gene CGG triplet repeat above 200 units in the 5' untranslated region of *FMR1,* leading to hypermethylation of the promoter region followed by transcriptional inactivation of the gene. FXS is caused by a loss of the fragile X mental retardation protein, which is believed to play a key role in early brain development and brain function.

Fragile X-Associated Disorders

Patients with a premutation (55-200 CGG repeats) may develop an *FMR1*-related disorder, such as fragile X–associated tremor or ataxia syndrome or, in women, fragile X–associated premature ovarian insufficiency (FXPOI). Fragile X–associated tremor or ataxia syndrome is a late-onset syndrome, comprising progressive development of intention tremor and ataxia, often accompanied by progressive cognitive and behavioral difficulties, including memory loss, anxiety, reclusive behavior, deficits of executive function, and dementia. FXPOI is characterized by ovarian failure before the 40 years of age.

Diagnosis
DNA studies are used to test for FXS. Cytogenetic testing was used before identification of the *FMR1* gene and is significantly less accurate than the current DNA test. Genotypes of individuals with symptoms of FXS and individuals at risk for carrying the variant can be determined by examining the size of the trinucleotide repeat segment and methylation status of the *FMR1* gene. Two main approaches are used: polymerase chain reaction (PCR) and Southern blot analysis.

PCR analysis uses flanking primers to amplify a fragment of DNA spanning the repeat region. Thus, the sizes of PCR products are indicative of the approximate number of repeats present in each allele of the individual being tested. The efficiency of PCR is inversely related to the number of CGG repeats, so large variants are more difficult to amplify and may fail to yield a detectable product in the PCR assay. This, and the fact that no information is obtained about *FMR1* methylation status, are limitations of the PCR approach. On the other hand, PCR analysis permits accurate sizing of alleles in the normal zone, the “gray zone,” and premutation range on small amounts of DNA in a relatively short turnaround time. Also, the assay is not affected by skewed X-chromosome inactivation.

The difficulty in fragile X testing is that the high fraction of GC bases in the repeat region makes it extremely difficult for standard PCR techniques to amplify beyond 100 to 150 CGG repeats. Consequently, Southern blot analysis is commonly used to determine the number of triplet repeats in FXS and methylation status. Alternatives to Southern blotting for determining FMR1 methylation status have been developed. They include methylation-sensitive PCR and methylation-specific melting curve analysis. One test currently available in Europe (FastFraX; TNR Diagnostics, Singapore) combines a direct triplet repeat-primed PCR with melting curve analysis for detecting CGG expansions. Asuragen offers the Xpansion Interpreter® test, which analyzes AGG sequences that interrupt CGG repeats and may stabilize alleles, protecting against expansion in subsequent generations. Asuragen also markets AmplideX® Fragile X Dx and Carrier Screen Kit, which is the first test approved by the U.S. Food and Drug Administration (FDA) (see Regulatory Status).

In 2011, a panel of genotyping reference materials for FXS was developed and is expected to be stable over many years and available to all diagnostic laboratories. A panel of five genomic DNA samples (normal female, female premutation, male premutation, male full mutation, and female full mutation) was endorsed by the European Society of Human Genetics and approved

as an International Standard by the Expert Committee on Biological Standardization at the World Health Organization.

The American College of Medical Genetics and Genomics (ACMG) released guidelines for testing in 2005, which were once again reviewed in 2013. These guidelines are reflected in this medical policy. In 2021, the ACMG released a revised technical standard on laboratory testing for fragile X. The authors noted that the new laboratory standards "are in general agreement" with the 2005 ACMG policy statement previously published.

Treatment
Current approaches to therapy are supportive and symptom-based. Psychopharmacologic intervention to modify behavioral problems in a child with FXS may represent an important adjunctive therapy when combined with other supportive strategies including speech therapy, occupational therapy, and special education services. Medication management may be indicated to modify attention deficits, impaired impulse control, and hyperactivity. Anxiety-related symptoms, including obsessive-compulsive tendencies with perseverative behaviors, also may be present and require medical intervention. Emotional lability and episodes of aggression and self-injury may be a danger to the child and others around him or her; therefore, the use of medication(s) to modify these symptoms also may significantly improve an affected child's ability to participate more successfully in activities in the home and school settings.

REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The Xpansion Interpreter® test is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. Until 2020, the FDA had chosen not to require any regulatory review of this test.

In February 2020, AmplideX® Fragile X Dx and Carrier Screen Kit (Asuragen) was granted a de novo 510(k) classification by the FDA. The new classification applies to this device and substantially equivalent devices of this generic type. AmplideX® Fragile X Dx and Carrier Screen Kit is cleared for diagnosis of FXS in conjunction with family history and clinical signs and symptoms. The test may also be used for carrier testing, but it is not indicated for fetal diagnostic testing, the screening of eggs obtained for in vitro fertilization prior to implantation, or stand-alone diagnoses of FXS. AmplideX® quantifies the number of CGG repeats in the *FMR1* alleles using PCR with gene-specific and triplet repeat primers followed by size resolution with capillary electrophoresis.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who have characteristics of FXS or an FXS-associated disorder, the evidence includes studies evaluating the clinical validity of FMR1 variant testing. Relevant outcomes are test accuracy, test validity, and resource utilization. The evidence demonstrates that FMR1 variant testing can establish a definitive diagnosis of FXS and fragile X−related syndromes when the test is positive for a pathogenic variant. Following a definitive diagnosis, the treatment of comorbid conditions may be improved. At a minimum, providing a diagnosis eliminates the need for further diagnostic workup. A chain of evidence supports improved outcomes following FMR1 variant testing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a personal or family history of FXS who are seeking reproductive counseling, the evidence includes studies evaluating the clinical validity of FMR1 variant testing and the effect on reproductive decisions. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. Testing the repeat region of the FMR1 gene in the context of reproductive decision making may include individuals with either a family history of FXS or a family history of undiagnosed intellectual disability, fetuses of known carrier mothers, or affected individuals or their relatives who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

V. DEFINITIONS TOP

N/A

VI. BENEFIT VARIATIONS TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations are based on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER TOP

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital

Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes								
81243	81244	0378U						

ICD-10-CM Diagnosis Codes	Description
E28.310	Symptomatic premature menopause
E28.319	Asymptomatic premature menopause
E28.39	Other primary ovarian failure
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F73	Profound intellectual disabilities
F79	Unspecified intellectual disabilities
F80.0	Phonological disorder
F80.1	Expressive language disorder
F80.2	Mixed receptive-expressive language disorder
F80.81	Childhood onset fluency disorder
F80.9	Developmental disorder of speech and language, unspecified
F82	Specific developmental disorder of motor function
F84.0	Autistic disorder
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F84.9	Pervasive developmental disorder, unspecified
F88	Other disorders of psychological development
Q99.2	Fragile X Chromosome

ICD-10-CM Diagnosis Codes	Description
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
Z36.0	Encounter for antenatal screening for chromosomal anomalies
Z36.2	Encounter for other antenatal screening follow-up
Z36.8A	Encounter for antenatal screening for other genetic defects
Z81.0	Family history of intellectual disabilities

IX. REFERENCES

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11. *US Food and Drug Administration. FDA Authorizes Marketing of the First Genetic Test to Aid in the Diagnosis of Fragile X Syndrome. February 21, 2020.*

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X. POLICY HISTORY

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MP 2.276	**11/20/2020 Consensus Review.** Policy statement unchanged. Background updated. References reviewed.
	07/19/2021 Consensus Review. Updated FEP, Background, and References. No changes to coding.
	02/21/2022 Consensus Review. Remove ICD-10 code F84.2. Updated cross references. Updated FEP, background, and references.

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	03/16/2023 Administrative Update. New Code 0378U added, effective 04/01/2023.
	10/18/2023 Consensus Review. No change to policy statement. Updated references. Coding reviewed, no changes.
	11/19/2024 Consensus Review. No change to policy statement. Updated references. Coding reviewed, no changes.

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