Medical Policy

Genetic Testing for Fragile X-Associated Disorders

Policy Number: OCA 3.571  
Version Number: 15  
Version Effective Date: 10/01/17

Product Applicability

- All Plan+ Products

Well Sense Health Plan
- New Hampshire Medicaid
- NH Health Protection Program

Boston Medical Center HealthNet Plan
- MassHealth
- Qualified Health Plans/ConnectorCare/Employer Choice Direct
- Senior Care Options ◊

Notes:
+ Disclaimer and audit information is located at the end of this document.
◊ The guidelines included in this Plan policy are applicable to members enrolled in Senior Care Options only if there are no criteria established for the specified service in a Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) on the date of the prior authorization request. Review the member’s product-specific benefit documents at www.SeniorsGetMore.org to determine coverage guidelines for Senior Care Options.

Policy Summary

Genetic testing for a fragile X-associated disorder is considered medically necessary for an adult or pediatric member with developmental delay, autism spectrum disorder with developmental delay, intellectual disability, and/or has an at-risk condition (as specified in the Medical Policy Statement section of this policy) and the Plan’s medical criteria are met. Plan prior authorization is required for all molecular and chromosomal genetic testing, except for prenatal genetic screening tests for a member with one of the pregnancy diagnosis codes specified in the Applicable Coding section of this policy when Plan criteria are met. Biochemical genetic tests used to study the amount or activity level...
of proteins to indicate changes to the DNA require prior authorization only when the test is included in the Applicable Coding section of a Plan genetic testing medical policy.

The Plan supports the National Comprehensive Cancer Network (NCCN) guidelines for genetic counseling for all genetic tests conducted with Plan members; NCCN recommends that adequate pre-test and post-test genetic counseling be provided by a health care professional with expertise in genetics. Genetic counseling provided to a Plan member (and/or guardian if the member is under the age of 18) should be documented in the member’s medical record and conducted by an appropriately trained practitioner with expertise and experience in genetics, including a provider acting within the scope of the provider’s license and practice, clinical geneticist, or genetic counselor.

See Plan policy, \textit{Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies} (policy number OCA 3.573), for Plan prior authorization guidelines for microarray analysis testing of an adult or pediatric member with unexplained intellectual disability, developmental delay, and/or multiple congenital anomalies. It will be determined during the Plan’s prior authorization process if the testing is considered medically necessary for the requested indication. See the Plan’s policy, \textit{Medically Necessary} (policy number OCA 3.14), for the product-specific definitions of medically necessary treatment.

Review Plan policy, \textit{Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening)}, policy number OCA 3.726, for medical guidelines for preimplantation genetic testing for fragile X syndrome; preimplantation genetic testing is a covered service for some BMC HealthNet Plan members, as specified in the member’s applicable benefit documents available at \url{www.bmchp.org}. See the following Plan policies for additional prior authorization guidelines for genetic testing available at \url{www.bmchp.org} for BMC HealthNet Plan members and \url{www.wellsense.org} for Well Sense Health Plan members:

1. \textit{Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies}, policy number OCA 3.573
2. \textit{Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests)}, policy number OCA 3.572
3. \textit{Genetic Testing for Familial Malignant Melanoma}, policy number OCA 3.78
5. \textit{Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome}, policy number OCA 3.57
6. \textit{Genetic Testing for Hereditary Colorectal Cancer}, policy number OCA 3.64
7. \textit{Genetic Testing for Hereditary Thrombophilia}, policy number OCA 3.728

\*Plan refers to Boston Medical Center Health Plan, Inc. and its affiliates and subsidiaries offering health coverage plans to enrolled members. The Plan operates in Massachusetts under the trade name Boston Medical Center HealthNet Plan and in other states under the trade name Well Sense Health Plan.
8. *Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening)*, policy number OCA 3.726

**Description of Item or Service**

**Testing for Fragile X-Associated Disorders:** DNA-based molecular analysis test that detects the fragile X mutation which is an expansion (lengthening) of trinucleotide repeats CGG within the FMR1 gene. Based on the test results, the patient is classified as normal, intermediate (or “gray zone”), premutation or full mutation based on the number of CGG repeats. Patients with a full mutation are considered affected with fragile X syndrome; those with a premutation are carriers and may have a FMR1-related disorder such as fragile X-associated primary ovarian insufficiency (FXPOI) or fragile X-associated tremor/ataxia syndrome (FXTAS).

**Medical Policy Statement**

The Plan considers genetic testing for a fragile X-associated disorder to be medically necessary when Plan medical criteria are met and documented in the adult or pediatric member’s medical record (with supporting documentation submitted to the Plan, as requested). Review Plan policy, *Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening)*, policy number OCA 3.726, rather than this policy for medical guidelines for preimplantation genetic testing for fragile X syndrome. Plan prior authorization may or may not be required when applicable criteria are met, as specified below in EITHER item A or item B:

A. **Prior authorization is required** when the member has a condition at risk for fragile X syndrome and is not pregnant. Genetic testing for fragile X is considered medically necessary when the member meets at least ONE (1) of the following criteria, as specified below in item 1 or item 2:

1. The results of the test will affect the member’s clinical management or the reproductive decisions of the member or the member’s parents, and the member (adult or pediatric member of any gender) has at least ONE (1) of the following **conditions at risk for fragile X syndrome**, as specified below in items a through c:

   a. Autism spectrum disorder with developmental delay;** OR
   b. Developmental delay;** OR
   c. Intellectual disability;** OR

   **Note:** The order of genetic testing is determined by the treating physician or a licensed practitioner (such as an advanced practitioner registered nurse or physician assistant when operating within the scope of the provider’s license) and may include chromosomal microarray analysis or genetic testing for fragile X-associated disorders.

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for a member with autism spectrum disorder with developmental delay, developmental delay, or intellectual disability when Plan criteria are met for the specified test. The Plan will authorize the first test requested by the treating physician or licensed practitioner when Plan criteria are met; the second test will be approved when Plan criteria are met if the first test is negative. See Plan policy, *Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies* (policy number OCA 3.573).

2. The results of the test will affect the member’s clinical management and the member has at least ONE (1) of the following risk categories for a fragile X-associated disorder, as specified in items a through d:

   a. Premature ovarian failure in a woman (including an individual born with female reproductive organs and/or with a typical female karyotype with two [2] X chromosomes); OR

   b. Late-onset tremor ataxia (FXTAS) in a member (regardless of gender); OR

   c. In fetus of known biological, carrier mother (including biological, carrier parent born with female reproductive organs and/or with typical female karyotype with two [2] X chromosomes), prenatal testing† of a fetus by amniocentesis or chorionic villus sampling is indicated following a positive fragile X carrier test in the mother (including positive carrier test with biological parent born with female reproductive organs and/or with typical female karyotype with two [2] X chromosomes); OR

   d. Member is planning a pregnancy and BOTH of the following criteria are met, as specified below as item (1) and item (2):

      (1) A positive result for fragile X genetic testing may influence future reproductive planning; AND

      (2) Member has a family history of fragile X syndrome with a family history defined as having at least ONE (1) affected first, second, and/or third degree relative; OR

†Note: See the list of services that do NOT require Plan prior authorization, as specified below in item B of this section and the Applicable Coding section of this policy.

B. **Prior authorization is NOT required** for prenatal genetic testing† on a pregnant member’s fetus for a fragile X-associated disorder when BOTH of the following criteria are met, as specified below in item 1 and item 2:

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*Genetic Testing for Fragile X-Associated Disorders*

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1. The pregnant member’s claim for the genetic screening test is submitted to the Plan according to BOTH of the following guidelines, as specified below in items a and b:

   a. The appropriate procedure code for fragile X-associated disorder testing is documented on the claim, as specified in the Applicable Coding section of this policy; AND

   b. One (1) of the pregnancy diagnosis codes specified in the Applicable Coding section of this policy is listed on the claim as the primary diagnosis for the member; AND

2. There is medical record documentation of medical necessity for the genetic screening test(s) for the pregnant member for targeted population-based screening which the Plan may validated with medical record audit rather than through the prior authorization process.

†Note: See the list of services that do NOT require Plan prior authorization, as specified in the Applicable Coding section of this policy.

Limitations

1. The Plan considers fragile X syndrome screening to be medically necessary for a member ONLY when applicable Plan criteria are met for testing, as specified in the Medical Policy Statement section of this policy. Indications for fragile X syndrome screening NOT considered medically necessary include testing an asymptomatic member, population-based screening of a member who is not in any of the specified risk categories, or a member with no family history (i.e., first degree, second degree, and/or third degree affected relative) of fragile X- associated disorder or a phenotype for fragile X-associated disorders (e.g., premature ovarian failure and underlying hormonal changes). Note: Prior authorization is NOT required for prenatal genetic testing on a pregnant member’s fetus for a fragile X-associated disorder when applicable criteria are met, as specified in item B of the Medical Policy Statement section and the Applicable Coding section.

2. A contraindication to genetic testing for a fragile X-associated disorder is testing a member with a previously known, not fragile X-associated cause of developmental delay, autism spectrum disorder with developmental delay, and/or intellectual disability; this includes previous results of abnormal chromosomal array analysis or other positive genetic test that provides explanation of the member’s condition not related to a fragile X-associated disorder. If genetic testing for a fragile X-associated disorder is requested for a member with a known, valid genetic diagnosis but a fragile X-associated disorder is still suspected as a second diagnosis, Plan Medical Director review is required.

3. The Plan considers the use of a single test that combines both chromosomal microarray analysis for autism spectrum disorders with testing of the FMR1 gene for fragile X syndrome to be experimental and investigational due to insufficient data on analytical validity, clinical validity,
and clinical utility; an example of such testing includes but is not limited to FirstStepDx PLUS (Lineagen Inc.).

4. The Plan considers a test using multiple–single nucleotide polymorphisms (SNPs) to identify the risk of autism spectrum disorders to be experimental and investigational due to insufficient data on analytical validity, clinical validity, and clinical utility; an example of such testing includes but is not limited to the ARISk2 Test (IntegraGen Inc.).

5. Multigene Panel Testing:

Advancements in technology have led a number of laboratories to develop multigene sequencing panels to diagnose X-linked intellectual disability; these panels vary in the types and number of genes based on the laboratory. Multigene panel testing uses next-generation sequencing technology to screen up to 114 genes on the X chromosome that have been associated with X-linked intellectual disability. Examples of X-linked intellectual disability multigene panels include but are not limited to the following: XLID Next-Gen Panel (Ambry Genetics Corp.), X-Linked Intellectual Disability Panel, Sequencing, 76 Genes (ARUP Laboratories), X-Linked Intellectual Disability: Sequencing Panel (Emory Genetics Laboratory), and X-Linked Intellectual Disability 60 Gene Next Generation Sequencing Panel (Emory Genetics Laboratory).

The use of a multigene testing panel is generally considered to be NOT medically necessary as an alternative to or in addition to variant testing of the FMR1 gene to identify a fragile X-associated disorder due to insufficient data on clinical validity and clinical utility of multigene testing. If the treating provider is recommending multigene panel testing rather than, or in addition to, the condition-targeted FMR1 testing specified in the Medical Policy Statement section of this policy, **Plan Medical Director review is required.** For multigene panel testing to be considered medically necessary, medical record documentation must be submitted to the Plan with the prior authorization request demonstrating that ALL of the following criteria are met (and after approval by a Plan Medical Director), with criteria specified below in items a through g:

a. A recommendation for multigene panel testing for the member by an independent board-certified or board-eligible Medical Geneticist, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory, or a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory; this provider has a documented evaluation of the member which includes a completed 3-generation pedigree and intends to engage in post-test follow-up counseling; AND
b. Member meets criteria for genetic testing outlined in the Medical Policy Statement section of this policy AND

c. All genes included in the multigene panel are relevant to the personal medical history, biological family medical history, and/or treatment plan for the member being tested and there are professional society management guidelines or National Comprehensive Cancer Network (NCCN) guidelines (with applicable references provided with the prior authorization request) documenting the clinical utility of testing for the members who test positive for any and all genes in the panel; AND

d. The results of the requested multigene panel will directly impact the treatment plan and clinical decision-making process for the member being tested; AND

e. There are no other known causative circumstances or factors (e.g., environmental exposures, injury, infection) that can explain the member’s symptoms or medical condition; AND

f. Multigene panel testing is more practical testing to diagnose the member’s condition than the separate single gene tests or targeted panels that would be recommended (with supporting documentation provided); AND

g. Clinical presentation of the member’s condition does not fit a well-described syndrome for which single-gene or targeted panel testing is available (e.g., comparative genomic hybridization/chromosomal microarray analysis) or single-gene or targeted panel testing is not clinically appropriate for the member’s condition (with supporting clinical documentation provided).

The Plan considers the multigene panel testing to be medically necessary only when ALL of the criteria outlined above (in items a through g) are met; disease-targeted genetic testing is considered medically necessary as an alternative when Plan criteria are met in the Medical Policy Statement section (and according to guidelines specified in the Limitations section of this policy). See the Genetic Testing Guidelines and Pharmacogenetics policy, policy number OCA 3.727, for guidelines related to multigene panel testing to determine response to drug metabolism and adjuvant therapy and the use of multigene panels to determine hereditary cancer susceptibility for other types of cancer.

The Genetic Testing Guidelines and Pharmacogenetics medical policy (policy number OCA 3.727) includes guidelines for genetic testing for additional indications that include but are not limited to the following: genetic testing for MECP2 sequence variants to diagnosis Rett syndrome and other disorders, testing using multiple—single nucleotide polymorphisms (SNPs) to identify the risk of autism spectrum disorders (e.g., ARISk2 Test from IntegraGen Inc.), whole exome sequencing, and whole genome sequencing. See Plan policy, Chromosomal Microarray Analysis for Unexplained Intellectual Genetic Testing for Fragile X-Associated Disorders

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Disabilities and/or Multiple Congenital Anomalies, policy number OCA 3.573, for indications for chromosomal microarray testing; indications not included in this Plan policy are included in the Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727.

Definitions

Autism Spectrum Disorder (ASD): A group of biologically based neurodevelopmental disorders characterized by impairments in three major domains: socialization, communication and behavior. It has been estimated that as many as 1 in 100 children are affected by ASD.

Chromosomal Microarray Analysis (CMA): Also known cytogenomic constitutional (genome-wide) microarray analysis or cytogenomic microarray analysis, CMA is a high-resolution, whole-genome screening used as a diagnostic tool to identify genetic abnormalities not detected with conventional cytogenetic analysis (e.g., karyotyping and FISH); CMA provides more refined testing by detecting smaller deletions and duplications in genomic material, potentially increasing the diagnostic yield in targeted populations. CMA collectively describes two (2) different laboratory techniques, comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays.

Developmental Delay: Failure to meet expected developmental milestones due to a significant delay in one (1) or more developmental skills, including gross or fine motor, speech/language, cognitive, social/personal, and/or adaptive development (e.g., activities of daily living or self care). A significant delay in two (2) or more of these developmental categories is considered global development delay and is thought to predict future intellectual disability. The term ‘developmental delay’ is used with children typically younger than five (5) years old.

Developmental Disorder/Developmental Disability: A severe, chronic disability of an individual that is attributable to a mental or physical impairment, or combination of mental and physical impairment, and is manifested before the individual attains the age of 22. The disability is likely to continue indefinitely, results in substantial functional limitations in three (3) or more of the following areas of major life activity: self-care, receptive and expressive language, learning, mobility, self-direction, capacity for independent living, and economic self-sufficiency. The disability reflects the individual's need for a combination and sequence of special, interdisciplinary, or generic services, individualized support or other forms of assistance that are of lifelong or of extended duration and are individually planned and coordinated. (Definition from the Developmental Disabilities Assistance and Bill of Rights Act of 2000, Public Law 106-402.)

First-Degree Relative: A blood relative of an individual who shares approximately 50% of their genes defined as a parent, full sibling, and children.

Fragile X-Associated Disorder: A genetic disorder caused by changes in the FMR1 gene, including fragile X syndrome, fragile X-associated tremor/ataxia syndrome, and fragile X-associated primary ovarian insufficiency. Genetic testing may be done on an individual’s DNA with a blood sample or from
the DNA of a fetus with a chorionic villus sampling (CVS), amniocentesis sample, or percutaneous umbilical cord blood sampling (PUBS).

**Fragile X-Associated Primary Ovarian Insufficiency (FXPOI):** A genetic condition in which the ovaries are not functioning at full capacity in an FMR1 premutation carrier. Common symptoms of FXPOI include absent or irregular periods, symptoms of menopause such as hot flashes, early menopause, and infertility.

**Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS):** A genetic neurodegenerative disorder in an FMR1 premutation carrier occurring more commonly in phenotypical males (including individuals with typical male karyotype with only one [1] X chromosome) than in phenotypical females (including individuals with typical female karyotype with two [2] X chromosomes). Most individuals have no related medical, developmental or neurological problems prior to the appearance of FXTAS symptoms, which usually occur after age 50. FXTAS symptoms include ataxia (balance problems), intention tremors, memory loss, mood instability, psychiatric symptoms, and cognitive decline.

**Fragile X Syndrome:** A genetic condition involving changes in part of the X chromosome. It is the most common form of inherited intellectual disability in males (including individuals with typical male karyotype with only one [1] X chromosome) and a significant cause of intellectual disability in females (including individuals with typical female karyotype with two [2] X chromosomes). Fragile X syndrome is caused by a change in the FMR1 gene. A small section of the gene code (CGG) is repeated on a fragile area of the X chromosome. The fragile X mutation involves an expanded number of the CGG repeats.

**Genetic Testing:** According to U.S. Library of Medicine, genetic testing is defined as a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person’s chance of developing or passing on a genetic disorder. More than 1,000 genetic tests are currently in use, and more are being developed. Several methods can be used for genetic testing:

1. Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.

2. Chromosomal genetic tests analyze whole chromosomes to see if there are large genetic changes, such as an extra copy of a chromosome or missing DNA, that cause a genetic condition.

3. Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

**Intellectual Disability (ID):** As stated by the American Association on Intellectual and Developmental Disabilities (AAIDD), intellectual disability is a disability originating before age 18 which is characterized...
by significant limitations both in intellectual functioning and in adaptive behavior (including conceptual, social, and practical adaptive skills). The degree of ID varies from one individual to another and may range from mild to profound. An individual's level of ID can be defined by their intelligence quotient (IQ) or by the amount and type of support they need. The term ‘intellectual disability’ generally applies to older children where IQ testing is valid and reliable. According to the American Academy of Pediatrics (AAP), the term ‘intellectual disability’ is suggested as an alternative term for ‘mental retardation.’

**Multigene Panel Tests:** Tests that evaluate more than one (1) gene simultaneously to detect changes in gene expression most commonly associated with certain diseases and other genes that may have limited evidence of an association to the disorder. Multigene panel tests may involve traditional exon-by-exon sequencing of targeted genes to identify genetic variants or use next-generation sequencing. Each laboratory establishes its own set of criteria for selecting the genes represented in a panel, even when panels are used for the same or similar clinical indications. The lack of regulatory oversight of genetic testing means that laboratories can change the components of a panel at any time, making it difficult to evaluate the clinical utility of multigene panel tests.

**Next-Generation Sequencing (NGS or Massively Parallel Sequencing):** Genetic testing that involves sequencing of millions of DNA fragments using the following three (3) levels of molecular analysis: (1) Disease-targeted gene panels to sequence genes with an established role in the targeted disease, (2) exome sequencing of coding regions of the genome to include less common variants associated with the disease (i.e., a coding region is the segment of a gene that contains a protein-coding sequence called an exon in all 22,000 genes of the human genome); and (3) genome sequencing of both the coding and non-coding regions of the genome (i.e., the non-coding regions in between exons are called introns). Multiple sequencing platforms and different processes result in variability in test results among laboratories.

**Second-Degree Relative:** A blood relative of an individual who shares approximately 25% of their genes defined as a grandparent, grandchildren, aunt, uncle, nephew, niece, and half-siblings.

**Single Nucleotide Polymorphisms (SNPs):** The most common type of genetic variation among individuals. Each SNP represents a difference in a single DNA building block, called a nucleotide. SNPs occur normally throughout a person’s DNA; normally these variations are found in the DNA between genes. If more than one (1) percent of a population does not carry the same nucleotide at a specific position in the DNA sequence, then this variation can be classified as a SNP. Most SNPs have no effect on health or development. When there is sufficient scientific evidence to support the clinical utility of testing, SNPs may help predict an individual’s response to certain drugs, susceptibility to environmental factors, risk of developing particular diseases, and/or susceptibility to genetic diseases within families.

**Third Degree Relative:** A blood relative of an individual who shares 12.5% of the individual’s genes as defined as a biological first cousin, great grandmother, or great grandfather.
X-linked Disorder: A chromosomal abnormality caused by mutations in genes on the X chromosome, one (1) of the two (2) sex chromosomes in each cell. In phenotypical females/individuals with two (2) X chromosomes, a mutation in one (1) of the two (2) copies of the gene in each cell is sufficient to cause an X-linked dominant disorder, and a mutation would have to occur in both copies of the gene to cause an X-linked recessive disorder. Because it is unlikely that phenotypical females (including individuals with typical female karyotype with two [2] X chromosomes) will have two (2) altered copies of this gene, phenotypical males (including individuals with typical male karyotype with only one [1] X chromosome) are affected by X-linked recessive disorders much more frequently than phenotypical females (including individuals with typical female karyotype with two [2] X chromosomes). The high clinical variability in female patients often makes the determination of an X-linked dominant disorder vs. an X-linked recessive disorder difficult. In phenotypical males (including individuals with typical male karyotype with only one [1] X chromosome), a mutation in the only copy of the gene in each cell causes an X-linked disorder. A characteristic of X-linked inheritance is that biological fathers (including biological parents with only one [1] X chromosome) cannot pass X-linked traits to their biological sons (including biological children with only one [1] X chromosome); this results in no phenotypical male-to-phenotypical male transmission. Examples of X-linked disorders include adrenoleukodystrophy, Alport syndrome, choroideremia, Fabry disease, fragile X syndrome, hemophilia A, hemophilia B, Hunter syndrome, incontinentia pigmenti, Lesch-Nyhan syndrome, muscular dystrophy, and X-linked intellectual disability. (Source: Genetic Home Reference from the U.S. Department of Health & Human Services.)

Whole Exome Sequencing (WES)/ Whole Genome Sequencing (WGS): WES captures and sequences at a deep level the protein coding regions (called exons) of an individual’s genes using first-generation sequencing techniques or next-generation sequencing to detect disease-causing variants and discover gene targets. While exons represent only 1% of the genome, they account for approximately 85% of disease-causing variants. Through identification of variants across the exome, WES avoids the need to run multiple single-gene tests, which require prior information about variants affecting the disease. WES has been performed in a number of cancers, whereby comparison between tumor DNA and normal DNA from the same individual allows identification of variants specific to the tumor, which may provide information used for diagnosis and treatment. WES is targeted sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses next-generation sequencing techniques to sequence both coding and non-coding regions of the genome. Because WES only evaluates the protein-coding regions of the human genome (exoms), WES is a more cost-effective alternative to WGS. WES produces a smaller, more manageable data set with faster turnaround time for analyses than WGS. WGS has the ability to detect structural variations located outside of the exome that may be related to many diseases and cannot be identified with WES. WES and WGS have been proposed to be more efficient than traditional sequencing methods in discovering the genetic causes of diseases, but there remain issues of error rates due to technical challenges and difficulty interpreting potential causative variants from variants of unknown significance generated for each patient. Examples of tests include but are not limited to the following: TruGenome tests (Illumina), Endometrial Cancer Panel (GeneDx), ExomeNext and ExomeNext-Rapid (Ambry Genetics), XomeDx™ test (GeneDx), mtSEEK Whole Mitochondrial.

Genetic Testing for Fragile X-Associated Disorders

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Genetic Testing for Fragile X-Associated Disorders

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Genome Analysis (Courtagen Life Sciences Inc.), and/or nucSEEK Comprehensive Sequence Analysis of Nuclear Mitochondrial Exome (Courtagen Life Sciences, Inc.). According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole genome or whole exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. See the Genetic Testing Guidelines and Pharmacogenetics medical policy (policy number OCA 3.727) rather than this policy for Plan guidelines related to WES and WGS.

Applicable Coding

The Plan uses and adopts up-to-date Current Procedural Terminology (CPT) codes from the American Medical Association (AMA), International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis codes developed by the World Health Organization and adapted in the United States by the National Center for Health Statistics (NCHS) of the Centers for Disease Control under the U.S. Department of Health and Human Services, and the Health Care Common Procedure Coding System (HCPCS) established and maintained by the Centers for Medicare & Medicaid Services (CMS). Because the AMA, NCHS, and CMS may update codes more frequently or at different intervals than Plan policy updates, the list of applicable codes included in this Plan policy is for informational purposes only, may not be all inclusive, and is subject to change without prior notification. Whether a code is listed in the Applicable Coding section of this Plan policy does not constitute or imply member coverage or provider reimbursement. Providers are responsible for reporting all services using the most up-to-date industry-standard procedure and diagnosis codes as published by the AMA, NCHS, and CMS at the time of the service.

Providers are responsible for obtaining prior authorization for the services specified in the Medical Policy Statement section and Limitation section of this Plan policy, even if an applicable code appropriately describing the service that is the subject of this Plan policy is not included in the Applicable Coding section of this Plan policy. Coverage for services is subject to benefit eligibility under the member’s benefit plan. Please refer to the member’s benefits document in effect at the time of the service to determine coverage or non-coverage as it applies to an individual member. See Plan reimbursement policies for Plan billing guidelines.

Plan prior authorization is required for all molecular and chromosomal genetic testing, except for prenatal genetic screening tests for a member with one of the Plan-specified, high-risk pregnancy diagnosis codes specified in the Applicable Coding section of this policy when Plan criteria are met. The medical necessity for genetic screening test(s) for the pregnant member for targeted population-based screening must be documented in the member’s medical record; the Plan may validated with medical record audit the medical necessity of genetic testing when the prior authorization requirement is waived. Prior authorization may or may not be required for medically necessary, non-invasive prenatal genetic screening, as specified below. See the following medical policies for additional prenatal genetic tests which do not require prior authorization according to Plan guidelines: Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital

Genetic Testing for Fragile X-Associated Disorders

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Plan-Specified, Routine and High-Risk Pregnancy ICD-10 Diagnosis Codes

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<tr>
<th>Code</th>
<th>Description</th>
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<td>Supervision of high risk pregnancy</td>
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<td>O28.5</td>
<td>Abnormal chromosomal and genetic finding on ante-natal screening of mother</td>
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<td>O35.0xx0 - O35.9xx9</td>
<td>Maternal care for known or suspected fetal abnormality and damage</td>
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<td>Maternal care for other fetal problems</td>
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<td>Z34.00 - Z34.93</td>
<td>Encounter for supervision of normal pregnancy</td>
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<td>Encounters for antenatal screenings</td>
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CPT Codes

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<tr>
<th>Code</th>
<th>Description</th>
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<td>81243</td>
<td>FMR1 (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles</td>
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<td>81244</td>
<td>FMR1 (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status)</td>
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<td>81401</td>
<td>Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
</tr>
</tbody>
</table>

Plan note: See Plan policy, Genetic Testing Guidelines and Pharmacogenetics (policy number OCA 3.727), for prior authorization guidelines for other tests included in this code.
### Clinical Background Information

Fragile X syndrome is a genetic condition characterized by moderate intellectual disability in affected males (including individuals born with male reproductive organs and/or with typical male karyotype with only one [1] X chromosome) and a spectrum of cognitive deficiencies in affected females (including individuals born with female reproductive organs and/or with typical female karyotype with two [2] X chromosomes) that include behavioral problems, learning disability mild or moderate intellectual disability. Males (including individuals born with male reproductive organs and/or with typical male karyotype with only one [1] X chromosome) may have a characteristic appearance (i.e., large head, long face, prominent forehead and chin, and protruding ears), connective tissue findings (i.e., joint laxity), and large testes (postpubertally). Behavioral abnormalities, sometimes including autism spectrum disorder, are also common.

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<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
</table>
| 81404 | Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)  
NLGN4X (neuroligin 4, X-linked) (e.g., autism spectrum disorders), duplication/deletion analysis  
Plan note: See Plan policy, *Genetic Testing Guidelines and Pharmacogenetics* (policy number OCA 3.727), for prior authorization guidelines for other tests included in this code. |
| 81405 | Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons), regionally targeted cytogenomic array analysis  
NLGN4X (neuroligin 4, X-linked) (e.g., autism spectrum disorders), full gene sequence  
Plan note: This CPT code includes numerous types of tests. See CPT® codebook for detailed description of this code. Review Plan policy, *Genetic Testing Guidelines and Pharmacogenetics* (policy number OCA 3.727), for additional Plan prior authorization guidelines. |
| 88248 | Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (e.g., for ataxia telangiectasia, Fanconi anemia, fragile X)  
According to the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG), cytogenomic microarray analysis and genetic testing for fragile X syndrome are designated as a first-line tests for generalized developmental delay and/or intellectual disability of an unknown etiology. Some children will present both with global developmental delay and clinical features of autism. The best approach to the diagnostic evaluation of these children is based on the judgment of the clinical geneticist and the treating provider.

Fragile X syndrome and other fragile X-associated disorders are caused by a change in the FMR1 gene. A small section of the gene code (CGG) is repeated on a fragile area of the X chromosome. The fragile X mutation involves an expanded number of the CGG repeats. According to the American College of Medical Genetics and Genomics (ACMG), CGG-repeat-expansion full mutations account for greater than 99% of cases of fragile X syndrome. Therefore, tests that effectively detect and measure the CGG repeat region of the FMR1 gene are greater than 99% sensitive. This test can be used for prenatal diagnosis in cells obtained from amniocentesis and chorionic villus sampling (CVS), with some variation in CVS results as compared with blood and amniocytes.

All genes, including the FMR1 gene are made up of a long series of chemicals called nucleotides, with each gene being unique. In the FMR1 gene in every person, there is a section in a region known as the 5'-untranslated region, in which there are a certain number of repeats of the three nucleotide sequence CGG. In healthy people, there are between 5 to 44 of these repeats. In patients with Fragile X syndrome, the repeats are generally between 200 to 2000. Individuals with between 55 to 200 repeats are said to have pre-mutations and are at risk for further expansion of the repeat length. They may also be at risk for conditions like premature ovarian failure or Fragile X associated tremor and ataxia syndrome (FXTAS).

Individuals who may benefit from genetic testing for fragile X syndrome include: children with symptoms of fragile X syndrome including developmental, speech, language, or motor delay; children or adults with a diagnosis of learning disabilities of unknown etiology, autism, autistic spectrum disorder, or pervasive developmental disorder, or intellectual disabilities. Individuals with a family history of fragile X syndrome, or intellectual disability or autism of unknown cause, may consider carrier testing to determine if they are at risk of transmitting the disease to future generations. Known carriers who are pregnant may consider prenatal genetic testing to determine if the fetus carries the sequence variant.

At the time of the Plan’s most recent policy review, the Centers for Medicare & Medicaid Services (CMS) has implemented the following national coverage determinations (NCDs) related to genetic tests: NCD for Colorectal Cancer Screening Tests (210.3) for coverage of immunoassay and guaiac fecal occult blood tests and the Cologuard™ - Multitarget Stool DNA (sDNA) test when CMS applicable criteria are met, NCD for Pharmacogenomic Testing for Warfarin Response (90.1) for medically necessary indications for testing as determined by CMS, and NCD for Cytogenetic Studies (190.3) for coverage based on CMS guidelines. Medicare uses a combination of national and local coverage.
determinations for making coverage decisions for genetic tests. Medicare administrative contractors (MAC) may implement local coverage determinations (LCDs) that apply only within their own jurisdictions. Verify if applicable CMS criteria are in effect (through an NCD, LCD, or other CMS guidelines) for the specified genetic test, product name, site-specific gene analysis, and the indication for testing on the date of the prior authorization request for a Senior Care Options member.

References


Genetic Testing for Fragile X-Associated Disorders

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Genetic Testing for Fragile X-Associated Disorders

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Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Colorectal Cancer Screening Tests (210.3). Effective Date October 9, 2014. Implementation Date September 8, 2015. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=281&ncdver=5&CoffeeSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=colorectal+cancer&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAABAAAAAAA%3d%3d&

Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Cytogenetic Studies (190.3). July 16, 1998. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=198&ncdver=1&CoffeeSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=cytogenetic&KeyWordLookUp=Title&KeyWordSearchType=And&Id=24308&Id_version=26&basket=Id*3a%24242308*3a%2426*3a%24Genetic+Testing*3a%24MAC+-+Part+B*3a%24Noridian+Administrative+Services%257C%257C+莹LLC+(03102)*3a%24&bc=gAAAAACAAA AAAAA%3d%3d&

Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response (90.1). August 3, 2009. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333&ncdver=1&CoffeeSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=warfarin&KeyWordLookUp=Title&KeyWordSearchType=And&Id=24308&Id_version=26&basket=Id*3a%24242308*3a%2426*3a%24Genetic+Testing*3a%24MAC+-+Part+B*3a%24Noridian+Administrative+Services%257C%257C+莹LLC+(03102)*3a%24&bc=gAAAAACAAA AAAAA%3d%3d&


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Hayes GTE Synopsis. devSEEK Sequence Analysis for Neurodevelopmental Disorders (Courtagen Life Sciences Inc.). Winifred Hayes, Inc. November 12, 2015.

Hayes GTE Synopsis. FirstStep\textsuperscript{DX} PLUS (Lineagen Inc.). Winifred Hayes, Inc. December 22, 2016.


Genetic Testing for Fragile X-Associated Disorders

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Genetic Testing for Fragile X-Associated Disorders


<table>
<thead>
<tr>
<th>Original Approval Date</th>
<th>Original Effective Date* and Version Number</th>
<th>Policy Owner</th>
<th>Original Policy Approved by</th>
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<tr>
<td>Regulatory Approval: N/A</td>
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<td>Internal Approval: 05/18/11: Medical Policy, Criteria, and Technology Assessment Committee (MPCTAC)</td>
<td>09/01/11 Version 1</td>
<td>Medical Policy Manager as Chair of MPCTAC</td>
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<td>06/30/11: Quality Improvement Committee (QIC)</td>
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*Effective Date for the BMC HealthNet Plan Commercial Product(s): 01/01/12
*Effective Date for the Well Sense Heath Plan New Hampshire Medicaid Product(s): 01/01/13
*Effective Date for the Senior Care Options Product(s): 01/01/16

Genetic Testing for Fragile X-Associated Disorders

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<table>
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<th>Summary of Revisions</th>
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<tr>
<td>12/01/11</td>
<td>Added new 2012 codes</td>
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<td>05/01/12</td>
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<td>clarify that a first degree relative is a biological parent, biological child, or</td>
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<td>biological sibling (rather than parent, child, or sibling).</td>
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<td>07/30/12</td>
<td>Off cycle review for Well Sense Health Plan. Revised Summary, Medical Policy Statement,</td>
<td>Version 4</td>
<td>08/03/12: MPCTAC</td>
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<td>Off cycle review for Well Sense Health Plan and merged policy format. Incorporate</td>
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<td>Definitions, Clinical Background Information, and References sections. Revised criteria</td>
<td>Version 7</td>
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<td>01/30/14</td>
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<td>04/01/14</td>
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<td>03/01/15</td>
<td>11/19/14: MPCTAC</td>
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<td>Updated criteria in the Medical Policy</td>
<td>Version 10</td>
<td>12/10/14: QIC</td>
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**Policy Revisions History**

<table>
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<td>Review for effective date 01/01/16. Updated template with list of applicable products and notes. Revised language in the Applicable Coding section.</td>
<td>01/01/16</td>
<td>11/18/15: MPCTAC 11/25/15: MPCTAC (electronic vote) 12/09/15: QIC</td>
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<td>09/28/16</td>
<td>Review for effective date 11/01/16. Administrative changes made to clarify language related to gender. Added definitions.</td>
<td>11/01/16</td>
<td>09/30/16: MPCTAC (electronic vote) 10/12/16: QIC</td>
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<td>01/01/17</td>
<td>Review for effective date 05/01/17. Revised ICD-10 pregnancy diagnosis codes in the Applicable Coding section. Updated criteria in the Limitations section. Revised Summary, Definitions, Clinical Background Information, References, and Reference to Applicable Laws and Regulations sections. Administrative changes made to the Medical Policy Statement section.</td>
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<td>Revision effective 10/01/17. Industry-wide updates to the ICD-10 diagnosis codes included in the Applicable Coding section.</td>
<td>10/01/17</td>
<td>Not applicable because industry-wide updates to ICD-10 diagnosis codes.</td>
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**Last Review Date**

01/01/17

**Next Review Date**

01/01/18
Authorizing Entity

MPCTAC

Other Applicable Policies

Medical Policy - *Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies*, policy number OCA 3.573
Medical Policy - *Experimental and Investigational Treatment*, policy number OCA 3.12
Medical Policy - *Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests)*, policy number OCA 3.572
Medical Policy - *Genetic Testing for Familial Malignant Melanoma*, policy number OCA 3.78
Medical Policy - *Genetic Testing Guidelines and Pharmacogenetics*, policy number OCA 3.727
Medical Policy - *Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome*, policy number OCA 3.57
Medical Policy - *Genetic Testing for Hereditary Colorectal Cancer*, policy number OCA 3.64
Medical Policy - *Genetic Testing for Hereditary Thrombophilia*, policy number OCA 3.728
Medical Policy - *Medically Necessary*, policy number OCA 3.14
Medical Policy - *Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening)*, policy number OCA 3.726

Reference to Applicable Laws and Regulations


Disclaimer Information: +

Medical Policies are the Plan’s guidelines for determining the medical necessity of certain services or supplies for purposes of determining coverage. These Policies may also describe when a service or supply is considered experimental or investigational, or cosmetic. In making coverage decisions, the Plan uses these guidelines and other Plan Policies, as well as the Member’s benefit document, and when appropriate, coordinates with the Member’s health care Providers to consider the individual Member’s health care needs.

Plan Policies are developed in accordance with applicable state and federal laws and regulations, and accrediting organization standards (including NCQA). Medical Policies are also developed, as appropriate, with consideration of the medical necessity definitions in various Plan products, review of current literature, consultation with practicing Providers in the Plan’s service area who are medical experts in the particular field, and adherence to FDA and other government agency policies. Applicable state or federal mandates, as well as the Member’s benefit document, take precedence over these guidelines. Policies are reviewed and updated on an annual basis, or more frequently as needed. Treating providers are solely responsible for the medical advice and treatment of Members.

The use of this Policy is neither a guarantee of payment nor a final prediction of how a specific claim(s) will be adjudicated. Reimbursement is based on many factors, including member eligibility and benefits on the date of service; medical

Genetic Testing for Fragile X-Associated Disorders

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necessity; utilization management guidelines (when applicable); coordination of benefits; adherence with applicable Plan policies and procedures; clinical coding criteria; claim editing logic; and the applicable Plan – Provider agreement.