Medical Policy

Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies

Policy Number: OCA 3.573
Version Number: 7
Version Effective Date: 05/01/17

Product Applicability

<table>
<thead>
<tr>
<th>All Plan* Products</th>
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<tbody>
<tr>
<td>Well Sense Health Plan</td>
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<tr>
<td>□ New Hampshire Medicaid</td>
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<td>□ NH Health Protection Program</td>
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<td>□ Qualified Health Plans/ConnectorCare/Employer Choice Direct</td>
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<tr>
<td>□ Senior Care Options ◊</td>
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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 using chromosomal microarray analysis (also known as cytogenomic microarray analysis) is considered medically necessary for an adult or pediatric member with unexplained intellectual disability, developmental delay, autism spectrum disorder with developmental delay, and/or multiple congenital anomalies when the Plan’s medical criteria are met. Requests for chromosomal microarray analysis for an indication not specified in this Plan policy (e.g., testing to diagnose genomic abnormalities in hematologic malignancies and/or response to drug therapy) will be reviewed using the Plan’s medical criteria included in the Genetic Testing Guidelines and Pharmacogenetics policy (policy number OCA 3.727). **Plan prior authorization is required for all Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies**

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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. 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, Genetic Testing for Fragile X-Associated Disorders (policy number OCA 3.571), for Plan prior authorization guidelines for genetic testing for a fragile X-associated disorder for an adult or pediatric member with developmental delay, autism spectrum disorder with developmental delay, and/or intellectual disability. 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, Medically Necessary (policy number OCA 3.14), for the product-specific definitions of medically necessary treatment.

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

1. Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests), policy number OCA 3.572
2. Genetic Testing for Familial Malignant Melanoma, policy number OCA 3.78
3. Genetic Testing for Fragile X-Associated Disorders, policy number OCA 3.571
4. Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727
5. Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome, policy number OCA 3.57
6. Genetic Testing for Hereditary Colorectal Cancer, policy number OCA 3.64

Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies

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7. **Genetic Testing for Hereditary Thrombophilia**, policy number OCA 3.728

8. **Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening)**, policy number OCA 3.726

### Description of Item or Service

**Chromosomal Microarray Analysis (CMA):** Also known as cytogenomic microarray analysis or cytogenomic constitutional (genome-wide) 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 (i.e., gains and losses in DNA), 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. In general, CMA offers the following advantages over conventional karyotyping: (1) CMA is more sensitive than karyotyping; (2) CMA decreases overall turnaround time and is less labor intensive than karyotyping; and (3) CMA uses standardized computerized analysis and is therefore less subject to human error than karyotyping. CMA can identify chromosomal aneuploidy and other large changes in the structure of chromosomes that would otherwise be identified by standard karyotype analysis, as well as submicroscopic abnormalities that are too small to be detected by karyotyping.

According to The American College of Obstetricians and Gynecologists (ACOG Committee Opinion Number 682), prenatal CMA may be used for a patient with a fetus with one (1) or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. In addition, ACOG recommends the use of CMA in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test’s increased likelihood of obtaining results and improved detection of causative abnormalities. Like conventional fetal karyotyping, prenatal CMA requires direct testing of fetal tissue and thus can be offered only with chorionic villus sampling or amniocentesis.

### Medical Policy Statement

The Plan considers chromosomal microarray analysis (CMA) to be medically necessary when the following medical criteria are met and documented in the member’s medical record (with supporting documentation submitted to the Plan, as requested) for an adult or pediatric member, as specified below in item A (when prior authorization is required) or item B (when prior authorization is not required). Review Plan policy, **Genetic Testing Guidelines and Pharmacogenetics**, policy number OCA 3.727, for chromosomal microarray analysis for indications not specified in this Plan policy.

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A. **Prior authorization is required** when the member is not pregnant and ONE (1) of the following applicable criteria must be met for chromosomal microarray analysis testing, as specified below in item 1 (criteria for first-line testing with initial chromosomal microarray analysis), item 2 (criteria for second-line testing with initial chromosomal microarray analysis), or item 3 (repeat chromosomal microarray analysis):

1. **First-Line Testing with Initial Chromosomal Microarray Analysis:**

   ALL of the following criteria are met, as specified below in items a through c:
   
   a. Testing is ordered by the treating physician or licensed practitioner (such as an advanced practitioner registered nurse or physician assistant) when operating within the scope of the provider’s license and the results of the test will affect the member’s clinical management; AND

   b. No specific genetic condition (including a fragile X-associated disorder) is suspected based on the member’s physical exam and/or family history; AND

   c. The member has at least ONE (1) of the following conditions with an **unknown etiology**, as specified below in items (1) through (4):

      (1) Two (2) or more major congenital anomalies; OR

      (2) Intellectual disability;* OR

      (3) Autism spectrum disorder with developmental delay;* OR

      (4) Development delay;* OR

2. **Second-Line Testing for Initial Chromosomal Microarray Analysis:**

   BOTH of the following criteria are met, as specified below in item a and item b:

   a. Testing is ordered by the treating physician or licensed practitioner (such as an advanced practitioner registered nurse or physician assistant) when operating within the scope of the provider’s license and the results of the test will affect the member’s clinical management; AND

   b. Initial chromosomal microarray analysis is conducted after genetic testing for fragile X-associated disorders when ONE (1) of the following criteria is met, as specified below in item (1) or item (2):

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(1) A member with intellectual disability,* autism spectrum disorder with developmental delay,* or developmental delay* has tested negative for a fragile X-associated disorder (FMR1 gene); OR

(2) A member with multiple (two or more) congenital anomalies, when the results are positive or negative for a fragile X-associated disorder (FMR1 gene). See Plan policy, Genetic Testing for Fragile X-Associated Disorder (policy number OCA: 3.571), for separate Plan medical criteria for genetic testing for fragile X-associated disorders.

* 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 for a member with intellectual disability, autism spectrum disorder with developmental delay, developmental delay, or multiple congenital anomalies with developmental delay when Plan criteria are met for the specified test. The Plan will authorize the first test requested by the treating physician or license 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, Genetic Testing for Fragile X-Associated Disorders (policy number OCA: 3.571).

3. Repeat Chromosomal Microarray Analysis:

Repeat chromosomal microarray analysis (CMA) is generally NOT considered medically necessary. If the treating provider is recommending a repeat CMA for a member (i.e., member has been tested with CMA in the past), Plan Medical Director prior approval is required. Medical record documentation must be submitted to the Plan with the prior authorization request demonstrating that ALL of the following criteria are met, as specified below in items a through e:

a. Applicable testing criteria are met, as specified above item 1 (First-Line Testing with Initial Chromosomal Microarray Analysis) or item 2 (Second-Line Testing for Initial Chromosomal Microarray Analysis) of this Medical policy Statement section; AND

b. Test results of the initial CMA conducted on the member (including methodology used); AND

c. Results of repeat CMA testing for the member will directly impact clinical decision-making and/or clinical outcome for the member being tested with an explanation of medical necessity for this additional testing; AND

d. Request for the repeat CMA uses a methodology that was not utilized in the previous CMA conducted with the member; AND

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e. The requested testing method to be used with the repeat CMA is considered scientifically valid for identification of the genetic abnormality, disorder or syndrome.

B. **Prior authorization is NOT required** for prenatal genetic testing on a pregnant member’s fetus for a chromosomal microarray analysis (CMA) when BOTH of the following criteria are met, as specified below in item 1 and item 2:

1. The pregnant member’s claim for the genetic screening test is submitted to the Plan with the following codes documented on the claim (as specified in the Applicable Coding section of this policy and items a and b below):

   a. The appropriate procedure code for CMA; AND

   b. One of the Plan-specified, high-risk pregnancy diagnosis codes specified in the Applicable Coding section of this policy is listed 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 validate with medical record audit rather than through the prior authorization process.

**Limitations**

1. The Plan considers chromosomal microarray testing experimental and investigational for ANY of the following indications, as specified below in item a or item b:

   a. For the diagnosis of chromosome abnormalities in the asymptomatic family members of individuals with previously identified chromosome abnormalities; OR

   b. For the diagnostic evaluation of purely behavioral problems (e.g., oppositional defiant disorder or personality disorders) and/or psychiatric diseases (e.g., schizophrenia or bipolar disorder.

   See the plan’s policy, *Experimental and Investigational Treatment* (policy number OCA: 3.12), for the product-specific definitions of experimental or investigational treatment.

2. Chromosomal microarray testing for the diagnostic evaluation of a member with autism spectrum disorder (ASD) without developmental delay requires Plan Medical Director review.

3. The Plan considers the use of a single test that combines both chromosomal microarray analysis for autism 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 FirstStep Dx PLUS (Lineagen Inc.).
Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies

See Plan policy, *Genetic Testing Guidelines and Pharmacogenetics*, policy number OCA 3.727, rather than this policy for Plan guidelines for other indications for chromosomal microarray testing, genetic testing for MECP2 sequence variants to diagnosis Rett syndrome and other disorders, criteria related to testing of multiple–single nucleotide polymorphisms (SNPs) to identify the risk of autism spectrum disorders (e.g., ARISk2 Test from IntegraGen Inc.), multigene panel testing, whole exome sequencing, and whole genome sequencing.

**Definitions**

**Autism Spectrum Disorders:** A group of neurodevelopmental disorders defined by measurable impairments in communication and social interactions, restricted interests and activities, and stereotypical behaviors.

**Balanced Rearrangements:** Chromosomes are organized in a different manner than expected but the standard amount of chromosome material is present (i.e., humans have 23 pairs of chromosomes for a total of 46 in each cell). Balanced chromosome rearrangements may occur when a piece of one chromosome has changed places with a piece of another chromosome, chromosomes stick together, or chromosome material is inverted. Unbalanced chromosome rearrangements occur when too little or too much chromosome material is present.

**Comparative Genomic Hybridization (CGH):** A molecular technique that is used to detect chromosome gain or loss by hybridizing DNA from a target cell and a normal cell. Chromosomal microarray analysis (CMA) is a method used to measure the gains and losses of DNA throughout the human genome; CMA includes both single nucleotide polymorphism (SNP) and CGH arrays.

**Congenital Anomaly:** A defect that is present at birth and may be the result of either environmental or genetic factors, or both.

**Copy Number Variants:** An alteration of the DNA of a genome that results in the cell having an abnormal number of copies of one (1) or more sections of the DNA.

**Cytogenetics:** A branch of genetic science that focuses on the study of the structure and function of the cell, especially the chromosomes. Cytogenetics includes but is not limited to G-banded karyotyping, fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH).

**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.)

FISH Analysis (Fluorescent In Situ Hybridization): Genetic test that uses fluorescent deoxyribonucleic acid (DNA) probes to identify small pieces of chromosomes that are missing or have extra copies. These small changes in chromosomes can be missed by the overall karyotype test. For example, FISH analysis can identify missing fragments of DNA on chromosome 22 found with velocardiofacial syndrome. FISH is used to detect the presence or absence of a particular segment of DNA, but can also give information as to the location of that DNA. 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).

FMR1-Related 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).

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.

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**Genome:** The entire set of genetic instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes, found in the nucleus, as well as a small chromosome found in the cells' mitochondria. These chromosomes, taken together, contain approximately 3.1 billion bases of DNA sequence.

**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.’

**Karyotype Analysis:** Genetic test to examine the number and basic structure of chromosomes in a sample of cells to identify genetic problems as the cause of a disorder or disease. Chromosomes are separated from cells, stained, and arranged in order from largest to smallest so that their number and structure of chromosomes can be studied under a light microscope. For example, karyotype can identify an extra copy of chromosome 21 found with Down syndrome. 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). Unlike chromosomal microarray analysis (CMA), karyotyping cannot identify submicroscopic abnormalities such as translocations, deletion or duplications.

**Major Congenital Anomalies:** Congenital anomalies or malformations that create significant medical problems for the patient or that require specific surgical or medical management. Major anomalies or malformations generally are not considered a variation of the normal spectrum.

**Mosaicism:** Mosaicism is a condition in which cells within the same person have a different genetic makeup. This condition can affect any type of cell. Mosaicism is caused by an error in cell division very early in the development of the fetus. Genetic testing can diagnose mosaicism and determine the type and severity of the disorder. Examples of mosaicism include: mosaic Down syndrome, mosaic Klinefelter syndrome, mosaic Turner syndrome.

**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. See the Genetic Testing Guidelines and Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies
Pharmacogenetics medical policy (policy number OCA 3.727) rather than this policy for Plan guidelines related to multigene panel testing.

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.

Sequence Inversions: The same sequence is present in reverse base pair order.

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. Chromosomal microarray analysis (CMA) is a method used to measure the gains and losses of DNA throughout the human genome; CMA includes both SNP and comparative genomic hybridization (CGH) arrays.

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

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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 (exons), 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 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 Stated 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:   Genetic
Testing for Fragile X-Associated Disorders, policy number OCA 3.571 4, and Genetic Testing Guidelines
and Pharmacogenetics, policy number OCA 3.727.

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<td>High-Risk</td>
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<td>Description:</td>
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<td>Prior authorization is NOT required for medically necessary</td>
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<td>prenatal genetic screening for chromosomal microarray analysis (with the CPT</td>
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<td>codes and/or HCPCS code specified below in this section) when one (1) of the</td>
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<td>following high-risk, pregnancy ICD-10 diagnosis codes is listed as the primary</td>
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<td>diagnosis code on the submitted claim and Plan criteria are met.</td>
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<td>Plan note: A mother may include a female member, a member born with female</td>
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<td>reproductive organs, and/or a member with a typical female karyotype including</td>
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<td>two (2) X chromosomes.</td>
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<td>O28.5</td>
</tr>
</tbody>
</table>

Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies

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### CPT Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description: Codes covered when medically necessary. Prior authorization is required for these CPT codes UNLESS billed with one (1) of the Plan-specified, high-risk pregnancy ICD-10 diagnosis codes listed above in this section as the primary diagnosis.</th>
</tr>
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<tbody>
<tr>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
</tr>
<tr>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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### HCPCS Code

<table>
<thead>
<tr>
<th>Code</th>
<th>Description: Code covered when medically necessary. Prior authorization is required for this HCPCS code UNLESS billed with one (1) of the Plan-specified, high-risk pregnancy ICD-10 diagnosis codes listed above in this section as the primary diagnosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3870</td>
<td>Comparative genomic hybridization (CGD) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability.</td>
</tr>
</tbody>
</table>

### Clinical Background Information

Chromosome abnormalities are a common cause of developmental delay (DD), intellectual disability (ID), multiple congenital anomalies (MCA), and other neurodevelopmental disorders. Traditional cytogenetic techniques (such as a karyotype analysis and FISH assays) use visualization and analysis of chromosomal rearrangements, including genomic gains and losses; conventional cytogenetic testing identifies a chromosome abnormality in fewer than 10% of individuals with clinical features suggestive of a genetic syndrome.
According to the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG), chromosomal microarray analysis and genetic testing for fragile X syndrome are designated as 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. The policy drafted by the Child Neurology Society states that "Microarray is the genetic test with the highest diagnostic yield in children with unexplained global developmental delay/intellectual delay."

Chromosomal microarray analysis, also known as comparative genomic hybridization (CGH), cytogenomic microarray analysis, and cytogenomic constitutional (genome-wide) microarray analysis, is able to detect variants with much higher resolution and is not reliant on staining and visual resolution limits found with conventional cytogenetic analysis. The test uses a gene chip or microarray to analyze various areas of the human genome for abnormal regions that contain too many or too few copies of the genetic material on each of the 46 chromosomes. CMA detects alterations in the genomic content of an individual (i.e., copy number variants [CNVs]). CNVs are chromosomal imbalances created as a result of the deletion and/or duplication of one or more sections of DNA. CMA compares the DNA content of the individual with a normal control individual to identify pathogenic CNVs that may be responsible for the suspected disorder. Tens of thousands to millions of different DNA fragments (probes) are attached to identifiable locations on a glass slide or gene chip. Array CGH (aCGH) is a variation of CGH that detects chromosomal abnormalities at a higher resolution than conventional CGH or chromosome-based CGH.

Chromosomal microarray analysis (CMA) provides more refined testing by detecting smaller deletions and duplications in entire genome, potentially increasing the diagnostic yield in targeted populations. CMA is not designed to detect balanced rearrangements in which there is no gain or loss of DNA (i.e., balanced inversions or balanced translocations); CMA does not detect small DNA sequence changes and low level mosaicism may be undetected. CMA is also being used a prenatal diagnostic tool as an alternative to karyotyping, requiring an invasive procedure to collect intact fetal cells (e.g., amniocentesis sample, chorionic villous sampling, or percutaneous umbilical cord blood sampling [PUBS]) or assessed using cell-free fetal DNA isolated from a maternal blood sample.

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


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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&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=colorectal+cancer&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAABAAA%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&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=cytogenetic&KeyWordLookUp=Title&KeyWordSearchType=And&lcd_id=24308&lcd_version=26&basketc=lcd*3a%2424308*3a%2426*3a%24Genetic+Testing*3a%24MAC+-+Part+B*3a%24Noridian+Administrative+Services%257C%257C+LLC+(03102)*3a%24&bc=gAAAAACAAA%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&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=warfarin&KeyWordLookUp=Title&KeyWordSearchType=And&lcd_id=24308&lcd_version=26&basketc=lcd*3a%2424308*3a%2426*3a%24Genetic+Testing*3a%24MAC+-+Part+B*3a%24Noridian+Administrative+Services%257C%257C+LLC+(03102)*3a%24&bc=gAAAAACAAA%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.


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Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies


Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies

<table>
<thead>
<tr>
<th>Original Approval Date</th>
<th>Original Effective Date* and Version Number</th>
<th>Policy Owner</th>
<th>Approved by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Approval: N/A</td>
<td>03/01/14 Version 1</td>
<td>Medical Policy Manager as Chair of Medical Policy, Criteria, and Technology Assessment Committee (MPCTAC) and member of Quality Improvement Committee (QIC)</td>
<td>MPCTAC and QIC</td>
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<td>Internal Approval: 11/20/13: MPCTAC 12/19/13: QIC</td>
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* Effective 03/01/14 to 04/30/16, the policy title was *Cytogenomic Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies*. Effective 05/01/16, policy renamed *Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies*.

*Effective date for Senior Care Options product(s): 01/01/16

### Policy Revisions History

<table>
<thead>
<tr>
<th>Review Date</th>
<th>Summary of Revisions</th>
<th>Revision Effective Date and Version Number</th>
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<tr>
<td>01/30/14</td>
<td>Off cycle review for effective date 04/01/14. Added ICD10 diagnosis code equivalents of existing ICD9 diagnosis codes.</td>
<td>04/01/14 Version 2</td>
<td>01/27/14: MPCTAC 01/30/14: QIC</td>
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<td>11/01/14</td>
<td>Review for effective date 03/01/15. Revised criteria in the Medical Policy Statement and Limitations sections. Updated the Summary, Description of Item or Service, Definitions, and Clinical Background Information sections. Revised review calendar.</td>
<td>03/01/15 Version 3</td>
<td>11/19/14: MPCTAC 12/10/14: QIC</td>
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<tr>
<td>11/25/15</td>
<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 Version 4</td>
<td>11/18/15: MPCTAC 11/25/15: MPCTAC (electronic vote) 12/09/15: QIC</td>
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<tr>
<td>01/01/16</td>
<td>Review for effective date 05/01/16. Revised language in the Applicable Coding section and updated the list of waived pregnancy diagnosis codes and corresponding procedure codes. Updated Summary, Description of Item or Service, Definitions, Clinical</td>
<td>05/01/16 Version 5</td>
<td>01/20/16: MPCTAC 02/10/16: QIC</td>
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### Policy Revisions History

<table>
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<tr>
<th>Date</th>
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<tr>
<td>09/28/16</td>
<td>Background Information, and References sections. Revised title. Revised criteria in the Medical Policy Statement and Limitations sections.</td>
<td>11/01/16</td>
<td>09/30/16: MPCTAC</td>
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<td>Review for effective date 11/01/16. Administrative changes to clarify language related to gender.</td>
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<td>(electronic vote)</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 Summary, Definitions, References, and Reference to Applicable Laws and Regulations sections. Updated criteria in the Medical Policy Statement section.</td>
<td>05/01/17</td>
<td>01/18/17: MPCTAC</td>
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<td>02/08/17: QIC</td>
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### Last Review Date
01/01/17

### Next Review Date
01/01/18

### Authorizing Entity
QIC

### Other Applicable Policies

- Medical Policy - *Experimental and Investigational Treatment*, policy number OCA 3.12
- Medical Policy - *Gene Expression Profiling of Tumor Tissue and Risk Stratification to Predict Cancer Recurrence (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 for Hereditary Breast and Ovarian Cancer Syndrome*, policy number OCA 3.57
- Medical Policy - *Genetic Testing for Hereditary Colorectal Cancer Syndrome*, 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 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.

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