# MEDICAL POLICY

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| MEDICAL POLICY DETAILS | |
|---|---|
| **Medical Policy Title** | **Chromosomal Microarray (CMA) Analysis for Prenatal Evaluation and Evaluation of Patients with Developmental Delay/ Intellectual Disability or Autism Spectrum Disorder** |
| **Policy Number** | **2.02.42** |
| **Category** | **Laboratory Test** |
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| **Product Disclaimer** | • *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.*<br>• *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.*<br>• *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.*<br>• *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*<br>• *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.* |

## POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, chromosomal microarray analysis (CMA) is considered **medically appropriate** for diagnosing a genetic abnormality in children with apparent nonsyndromic cognitive developmental delay/intellectual disability (DD/ID) or autism spectrum disorder (ASD), according to accepted Diagnostic and Statistical Manual of Mental Disorders-5$^{th}$ edition criteria, or multiple anomalies not specific to a well-delineated genetic syndrome, when **ALL** of the following conditions are met:

   A. Any indicated biochemical tests for metabolic disease have been performed, and results are non-diagnostic;

   B. FMR1 gene analysis (for Fragile X), when clinically indicated, is negative;

   C. The results from the genetic testing have the potential to impact the clinical management of the patient; and

   D. Testing is requested after the parent(s) has/have been engaged in face-to-face genetic counseling with a healthcare professional who has appropriate genetics training and experience

II. Based upon our criteria and assessment of the peer-reviewed literature, CMA is considered **investigational** in all other cases of suspected genetic abnormality in children with DD or ASD.

III. Based upon our criteria and assessment of the peer-reviewed literature, CMA to confirm the diagnosis of a disorder or syndrome that is routinely diagnosed based on clinical evaluation alone is considered **not medically necessary**.

IV. Based upon our criteria and assessment of the peer-reviewed literature, CMA for prenatal testing, when performed by a qualified laboratory and offered in a setting with adequately trained health care providers to provide appropriate pre-

and post-test genetic counseling, is considered **medically appropriate** in pregnant patients who are undergoing invasive prenatal diagnostic testing.

*Refer to Corporate Medical Policy #2.02.03 Genetic Testing for Inherited Disorders.*

*Refer to Corporate Medical Policy #4.01.03 Prenatal Genetic Testing.*

*Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services.*

## POLICY GUIDELINES

I. The American College of Medical Genetics (ACMG) Guideline, Evaluation of the Newborn with Single or Multiple Congenital Anomalies, includes the following definitions:

   A. A malformation refers to abnormal structural development.

   B. A major malformation is a structural defect that has a significant effect on function or social acceptability. Example: ventricular septal defect or a cleft lip.

   C. A minor malformation is a structural abnormality that has minimal effect on function or societal acceptance. Examples: preauricular ear pit or partial syndactyly (fusion) of the second and third toes.

   D. A syndrome is a recognizable pattern of multiple malformations. Syndrome diagnoses are often relatively straightforward and common enough to be clinically recognized without specialized testing. Examples include Down syndrome, neural tube defects and achondroplasia. However, in the very young, or in the case of syndromes with variable presentation, confident identification may be difficult without additional testing.

II. If the genetic test is being performed for knowledge only, and that knowledge will not alter management or treatment of the patient or family member, then the testing is **not medically appropriate**.

III. If there is a high clinical likelihood that the patient has a specific disorder, and the treatment will not be modified based on the genetic testing results, then the testing is **not medically appropriate**.

IV. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.

V. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

VI. Genetic testing coverage is contract-dependent. Please contact your local Customer Care (Member/Provider) Department, to determine coverage under a member's subscriber contract.

## DESCRIPTION

Children with signs of neurodevelopmental delays or disorders in the first few years of life may eventually be diagnosed with intellectual disability, autism syndromes, or serious and lifelong conditions that present significant challenges to families and to public health. Cases of developmental delay/intellectual disability (DD/ID) and of autism spectrum disorder (ASD) may be associated with genetic abnormalities. For children with clear, clinical symptoms and/or physiologic evidence of syndromic neurodevelopmental disorders, diagnoses are based primarily on clinical history and physical examination, and then may be confirmed with **targeted** genetic testing of *specific genes* associated with the diagnosed syndrome. However, for children who do not present with an obvious syndrome, who are too young for full expression of a suspected syndrome, or who may have an atypical presentation, genetic testing may be used as a basis for establishing a diagnosis.

Chromosomal Microarray (CMA) or array of Comparative Genomic Hybridization (aCGH) has been proposed as a diagnostic tool for individuals who have unexplained developmental disabilities, autism disorders or congenital anomalies that cannot be confirmed by clinical presentation or through conventional genetic testing. While conventional cytogenetic analysis (e.g., G-banded karyotype, specific FISH assays, and subtelomeric screening) is limited by its low resolution and low diagnostic yield, CMA/aCGH allows for detection of smaller, clinically significant genetic abnormalities not detectable by conventional assays, thus improving resolution and diagnostic yield. These genetic abnormalities, expressed as copy number variants (CNVs), are described as deletions and duplications of large segments of genomic material. CNVs may be classified as abnormal, benign, or variations of unknown significance (VUS). Abnormal CNVs are identified for many well-established syndromes where the type and location of the chromosomal abnormality is known. Benign CNVs are usually inherited from a healthy parent. VUS are new chromosomal abnormalities that require additional study, including a detailed family history and familial genetic testing to determine their significance.

Prenatal fetal karyotyping is a routine test initiated when a fetus is believed to be at high risk for a chromosomal abnormality due to a structural abnormality identified during an ultrasound exam, family history, or other reasons agreed on by the patient and physician. However, karyotyping provides useful information in only a small percentage of these cases. Consistent with the increased diagnostic yield of CMA analysis, many laboratories are now providing this service in the prenatal setting. Currently, the microarrays used in this setting are most often targeted arrays used to reduce the number of results of uncertain significance, ~~and,~~ thus reduce parent anxiety and difficulties in decision-making. However, whole-genome analysis is also available.

## RATIONALE

The American College of Obstetrics and Gynecology (ACOG) Committee on genetics published a statement on the use of microarrays and next-generation sequencing technology in obstetrics and gynecology. The committee recommended CMA testing for individuals with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis, and in individuals with a structurally normal fetus undergoing invasive prenatal diagnostic testing, replacing the need for karyotyping. The use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older, as most genetic mutations identified by chromosomal microarray analysis are not associated with increasing maternal age. Because there is improved detection of causative abnormalities with CMA testing, in cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired, chromosomal microarray analysis on fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended. The committee emphasized that comprehensive patient pre-test and post-test genetic counseling from qualified personnel such as a genetic counselor or geneticist regarding the benefits, limitations, and results of CMA is essential. CMA should not be ordered without informed consent, which should be documented in the medical record and include discussion of the potential to identify findings of uncertain significance, non-paternity, consanguinity, and adult-onset disease.

The American College of Medical Genetics and Genomics (ACMG) released a technical standard in 2021 to assist clinical laboratories in validating CMA methodologies. ACMG names CMA as a first-tier test for evaluating chromosomal imbalances associated with intellectual disability, autism, and/or multiple congenital anomalies. Furthermore, CMA is recommended for patients undergoing invasive prenatal diagnosis with one or more major fetal structural abnormalities identified by ultrasonographic examination, and in the evaluation of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired (Shao, 2021).

The American Academy of Pediatrics stated that CMA should now be considered a first-tier diagnostic test in all children for whom the causal diagnosis is not known in their clinical report from 2014 and reaffirmed in 2020 (Moeschler, 2014). CMA is now the standard for diagnosis of patients with global developmental delay/intellectual delay (GDD/ID), as well as other conditions, such as ASDs and multiple congenital anomalies. Specific metabolic testing should be considered. Fragile X testing should be performed in all cases.

As a prenatal screening tool, CMA is able to detect copy number variations (CNVs), but interpretation of the results is often difficult because not all CNVs are pathological. Many CNVs are associated with variable clinical phenotypes, or are

benign, or are considered variations of unknown significance (VOUS). Consequently, interpretation of results can be problematic, genetic counseling may be challenging, and parental anxiety may increase, which could potentially result in termination of a healthy fetus. To reduce the number of observed indeterminate CNVs observed, CMA may be targeted to specific well--characterized diagnostic areas or lower resolution arrays may be used. Only a few studies with a large number of fetal samples have been reported that show CMA identifying additional CNVs compared to conventional karyotyping. The largest increase is noted in pregnant women with advanced maternal age or when abnormalities in ultrasound were detected. Current literature continues to evolve as the database for CNVs continues to expand thus CMA for prenatal screening or diagnosis is considered promising.

In 2015, AHRQ published a report on Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder. Highlights of the summary include the following: "scientific advances in recent decades have led to the discovery of genetic abnormalities that may explain the reasons for many developmental disabilities (DD) cases. A large number of genetic tests have been developed and adopted in clinical practice. These tests are used to differentiate well-defined DD syndromes (e.g., fragile X syndrome, Rett syndrome) or, more commonly, to establish an etiologic diagnosis for unexplained intellectual disability (ID), autism spectrum disorder (ASD), or global developmental delay (GDD). These tests employ a broad range of methods, including next-generation sequencing, Sanger sequence analysis, microarray, comparative genomic hybridization, single nucleotide polymorphism detection, multiplex ligation-dependent probe amplification, and other polymerase chain reaction-based tests. These tests analyze a single gene, a chromosome, a chromosomal region, or the whole genome or exome".

As genetic tests have become increasingly available, payers have observed a rapid diffusion of these tests in health care. Some tests (e.g., microarray-based aCGH have been recommended by professional groups as first-tier diagnostic tests for DDs. The proposed benefits of genetic testing include providing an improved sense of empowerment for patient families, refining treatment options, providing prognosis, preventing comorbidities, avoiding unnecessary diagnostic tests, providing recurrence-risk-based counseling, and improving access to needed support or services. However, these proposed benefits need to be validated by clinical studies.

The AHRQ report focused on evidence directly linking genetic testing to changes in health outcomes. However, the search did not identify any study – randomized or nonrandomized – in that category. This was considered a major gap that needs to be filled by future research. Randomized, controlled trials (RCTs) and well-designed non-randomized studies that directly compare health outcomes for use versus no use of the tests is the ideal type of study for addressing clinical utility. However, conducting these studies, particularly RCTs, can be difficult for various practical reasons. Because the genetic testing area changes so quickly, the test being studied may become obsolete even before long-term data are available. Other practical challenges for conducting clinical utility trials also exist, such as difficulty in patient recruitment (particularly for rare disorders) and high expense associated with the studies. Regardless of these challenges, it may still be feasible to design and execute clinical utility trials for certain tests and disorders, and researchers are encouraged to make an effort in that direction.

More studies should be performed to assess genetic tests' value perceived by families affected by DDs or addressing the impact of genetic testing on clinical management or family decisions, particularly parents' views on the importance of determining etiology and how to counsel them on the value of etiologic evaluation. This enhances our understanding of genetic tests' potential to cause changes in health outcomes (e.g., psychosocial outcomes).

In the context of DD care, genetic testing is often used to establish an etiologic diagnosis rather than establish a clinical diagnosis. However, researchers may not always agree on whether a genetic aberration (e.g., certain type of copy number variants) is "causal," "pathogenic," or "clinically significant." Several public information sources exist to facilitate the identification of causal genetic aberrations. A more robust framework for evaluating which variants play a role in disease and are relevant to patient care is needed.

## CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*

- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

**CPT Codes**

| Code | Description |
|---|---|
| 81228 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis |
| 81229 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis |
| 81349 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis |
| 81425 | Genome (eg, unexplained constitution or heritable disorder or syndrome); sequence analysis |
| 81426 | Genome (eg, unexplained constitution or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (list separately in addition to code for primary procedure) |
| 81427 | Genome (eg, unexplained constitution or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome) |
| 81470 | X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, AND SLC16A2 |
| 81471 | X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2 |
| 0322U | Neurology (autism spectrum disorder [ASD]), quantitative measurements of 14 acyl carnitines and microbiome-derived metabolites, liquid chromatography with tandem mass spectrometry (LC-MS/MS), plasma, results reported as negative or positive for risk of metabolic subtypes associated with ASD (NPDX ASD Test Panel III, Stemina Biomarker Discovery d/b/a NeuroPointDX( (effective 04/01/2022) |



**HCPCS Codes**

| Code | Description |
|---|---|
| S3870 | Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability |

**ICD10 Codes**

| Code | Description |
|---|---|
| E78.71-E78.79 | Disorders of bile acid and cholesterol metabolism (code range) |
| F70-F79 | Intellectual disabilities (code range) |
| F84.0 | Autistic disorder |
| G90.1 | Familial dysautonomia (Riley-Day) |
| P29.3-P29.38 | Persistent fetal circulation (code range) |
| Q00.0-Q07.9 | Congenital malformations of brain (code range) |
| Q10.0-Q15.9 | Congenital malformations of eyelid (code range) |
| Q16.0-Q17.9 | Congenital malformations of ear (code range) |
| Q18.0-Q18.9 | Congenital malformations of face and neck (code range) |
| Q20.0-Q28.9 | Congenital malformations of cardiac chambers and connections (code range) |
| Q30.0-Q34.9 | Congenital malformations of nose and respiratory system (code range) |
| Q38.0-Q45.9 | Congenital malformations of digestive system (code range) |
| Q50.01-Q56.4 | Congenital malformations of male and female reproductive organs (code range) |
| Q60.0-Q64.9 | Congenital malformations of urinary system (code range) |
| Q65.00-Q79.9 | Congenital malformations of limb(s) (code range) |
| Q80.0-Q82.9 | Congenital malformations of skin (code range) |
| Q90.0-Q99.9 | Chromosomal abnormalities (code range) |
| Z13.4 | Encounter for screening for certain developmental disorders in childhood |
| Z13.71-Z13.79 | Encounter for screening for genetic and chromosomal anomalies (code range) |
| Z13.810-Z13.818 | Encounter for screening for other specified diseases and disorders (code range) |
| Z13.828 | Encounter for screening for other musculoskeletal disorder |
| Z13.84 | Encounter for screening for dental disorders |
| Z13.89 | Encounter for screening for other disorder |
| Z13.9 | Encounter for screening, unspecified |
| Z36 | Encounter for antenatal screening of mother |

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*Key Article

## KEY WORDS

Chromosome microarray analysis, comparative genomic hybridization array, genetic analysis for development delay, intellectual delay, or autism spectrum disorders.

## CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=133&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AAgAAAQBIAAA&

There is currently a Local Coverage Article (LCA) for Molecular Pathology Procedures. Please refer to the following LCA website for Medicare members: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56199&ver=73&LCDId=35000&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AAgAAAQBIAAA&=