MEDICAL POLICY

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**
Current Effective Date	**November 20, 2025**
Next Review Date	**November 2026**

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Comparative genomic hybridization (CGH)/ chromosomal microarray analysis (CMA) is considered **medically appropriate** for:

A. Diagnosing a child with:

1. Apparent nonsyndromic cognitive developmental delay/intellectual disability (DD/ID);
2. Autism spectrum disorder (ASD); **or**
3. Multiple anomalies not specific to a well-delineated genetic syndrome;

AND

B. When **BOTH** of the following conditions are met;

1. Any indicated biochemical tests for metabolic disease have been performed, and results are non-diagnostic; **and**
2. 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. CMA is considered **medically appropriate** in pregnant patients who are undergoing invasive prenatal diagnostic testing when **BOTH** of the following criteria are met:

A. Testing is performed by a qualified laboratory; **and**

B. Testing is offered in a setting with adequately trained health care providers to provide appropriate pre-and post-test genetic counseling.

III. 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. CMA is considered **investigational** in all other cases of suspected genetic abnormality in children with other forms of delayed development, including but not limited to, idiopathic growth or language delay.

RELATED POLICIES

Corporate Medical Policy

2.02.03 Genetic Testing for Inherited Disorders

2.02.46 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

4.01.03 Prenatal Genetic Testing

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

I. 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 or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Supporting Documentation Required

The following factors will be considered when determining the medical appropriateness of a genetic test:

A. There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.

B. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.

C. The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).

D. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.

E. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any CGH/CMA. If targeted testing has not been performed, rationale as to why CGH/CMA is medically necessary should be documented.

V. 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.

VI. Global developmental delay is defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) as the failure to meet expected developmental milestones in several areas of intellectual functioning in an individual younger than five (5) years who cannot undergo systematic assessment of intellectual functioning, including children too young to participate in standardized testing.

VII. Intellectual disability is defined in the DSM-5 as significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills in individuals five (5) years or older.

DESCRIPTION

Chromosomal microarray analysis is a method of genetic testing that may identify small deletions and duplications of the sub-telomers, each pericentromeric region and other chromosome regions. It is being investigated for the screening, diagnosis and treatment of congenital anomalies, autism spectrum disorder, developmental delays, and screening for prenatal gene mutations.

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, thus reduce parent anxiety and difficulties in decision-making. However, whole-genome analysis is also available.

SUPPORTIVE LITERATURE

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.

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.

Miller et al (2018) published a foundational study that established CMA as a first-line diagnostic tool for individuals with developmental delay (DD), intellectual disability (ID), and autism spectrum disorder (ASD). The International Standard Cytogenomic Array (ISCA) Consortium held two international workshops and conducted a literature review of 33 studies, including 21,698 patients tested by CMA. The diagnostic yield of CMA in these populations was reported to be 15–20%, significantly higher than that of conventional karyotyping. The study emphasized CMA's ability to detect clinically relevant CNVs that are often missed by traditional cytogenetic methods, reinforcing its value in uncovering the genetic basis of unexplained neurodevelopmental disorders.

Zhang et al (2020) reported on a retrospective study of 477 prenatal cases both karyotyping and chromosomal microarray analysis (CMA) were performed to evaluate their diagnostic effectiveness. CMA identified 71 chromosomal abnormalities (15.88%), while traditional karyotyping detected only 23 abnormalities (5.15%). Notably, CMA revealed 3.80% pathogenic copy number variants (pCNVs) and 6.93% variants of unknown significance (VOUS). CMA detected 3.8% more abnormalities than karyotyping alone, highlighting its superior sensitivity. The detection rate of chromosomal abnormalities and VOUS was significantly higher in fetuses with ultrasound anomalies ($P < 0.01$), reinforcing CMA's value in high-risk pregnancies. These findings support CMA as a first-tier diagnostic tool in prenatal genetic evaluation, especially when fetal structural anomalies are present.

Chang et al (2025) conducted a systematic review and meta-analysis that assessed the diagnostic effectiveness of genetic testing methods— CMA, whole exome sequencing (WES), and whole genome sequencing (WGS)—in individuals with neurodevelopmental disorders (NDDs) and epilepsy. Drawing from 416 studies and over 124,000 participants, the analysis revealed that WES had the highest diagnostic yield, identifying pathogenic variants in 35.3% of NDD cases and 34.2% of epilepsy cases. CMA, while still valuable, showed lower yields of 14.8% for NDDs and 13.3% for epilepsy. Subgroup analyses highlighted significantly higher yields in individuals with dysmorphic features (54.7%), syndromic presentations (37.6%), co-occurring epilepsy (35.6%), and early-onset or drug-resistant epilepsy (32.3%). These findings support the growing preference for next-generation sequencing (NGS) technologies, particularly WES and WGS, as first-line diagnostic tools in clinical genetics, while CMA remains useful for detecting copy number variants.

PROFESSIONAL GUIDELINE(S)

The American Academy of Pediatrics published a clinical report in 2025 (Rodan et al) that provides a comprehensive framework for providers to assess children with developmental concerns. The report states that evaluation should begin with a pheno-type driven approach, using clinical features, family history and corollary testing to narrow the differential diagnosis. If no specific disorder is suspected, an agnostic approach is recommended, starting with exome or gene sequencing and chromosome microarray as first-tier tests. Fragile X testing is highlighted as a key component, especially when family history suggests features like premature ovarian failure or tremor/ataxia.

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 (2016; reaffirmed 2025). 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 (Shao 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.

ACMG released a practice guideline in 2010 (reaffirmed in 2020) on array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. ACMG states that CMA testing for copy number variants was recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

I. Multiple anomalies not specific to a well-delineated genetic syndrome,

II. Apparently nonsyndromic developmental delay/intellectual disability,

III. Autism spectrum disorder (ASD)

The American Academy of Neurology and the Child Neurology Society published an evidence report on genetic and metabolic testing on children with global developmental delay (Michelson 2011). The report concluded that CMA testing has the highest diagnostic yield in children with developmental delay/intellectual disability, that the "often complex results require confirmation and careful interpretation, often with the assistance of a medical geneticist," and that CMA should be considered the "first-line" test. The guidelines acknowledged that "research is sorely lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis."

The Agency for Healthcare Research and Quality (AHRQ) published a report on Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder (Sun 2015). 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."

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. Since 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.

REGULATORY STATUS

The United States Food and Drug Administration (FDA) provides oversight of laboratory developed tests, now considered medical devices under the Federal Food, Drug, and Cosmetic Act. Refer to the FDA Medical Device website. Available from: https://www.fda.gov/medical-devices [accessed 2025 Oct 17]

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

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
0209U (E/I)	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes, and areas of homozygosity for chromosomal abnormalities (CNGnome, PerkinElmer Genomics)

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)
P29.30-P29.38	Persistent fetal circulation (code range)
Q00.0-Q07.9	Congenital malformations of brain, spinal cord and nervous system (code range)
Q10.0-Q15.9	Congenital malformations of eye~~lid~~ (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, valves, connections and circulatory system (code range)
Q30.0-Q34.9	Congenital malformations of nose, airway 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 skeletal and musculoskeletal system (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

Code	Description
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
Z36.0-Z36.9	Encounter for antenatal screening (code range)

REFERENCES

ACOG Committee on Genetics [Internet]. ACOG Committee Opinion No. 682: Microarray and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. December 2016; reaffirmed 2025 [accessed 2025 Aug 01] Available from: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2016/12/microarrays-and-next-generation-sequencing-technology-the-use-of-advanced-genetic-diagnostic-tools-in-obstetrics-and-gynecology

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Sun F, et al. Genetic testing for developmental disabilities, intellectual disability, and autism spectrum disorder [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 Jun. (Technical Briefs, No. 23.) [Accessed 2025 October 17]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK304462

Zhang Y, et al. Application of chromosomal microarray analysis in prenatal diagnosis: a retrospective study of 477 cases. BMC Pregnancy Childbirth. 2020;20(1):743.

SEARCH TERMS

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

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Based on our review, Chromosomal Microarray (CMA) Analysis is not addressed in National Medicare coverage determinations or policies.

LCD - Molecular Pathology Procedures (L35000) [accessed 2025 Oct 17]

Article - Billing and Coding: Molecular Pathology Procedures (A56199) [accessed 2025 Oct 17]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- 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.
- 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.
- 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 HISTORY/REVISION	
Committee Approval Dates	
11/17/11, 11/15/12, 12/19/13, 12/18/14, 11/19/15, 11/17/16, 11/16/17, 12/20/18, 12/19/19, 12/17/20, 12/16/21, 12/22/22, 12/21/23, 12/19/24, 11/20/25	
Date	**Summary of Changes**
11/20/25	• Annual review; policy statements reformatted. Policy criteria for FMR1 gene analysis was removed as it is no longer required. Removal of the following policy criteria: "The results from the genetic testing have the potential to impact the clinical management of the patient, (e.g., no repeat testing)."
01/01/25	• Summary of changes tracking implemented.
01/20/11	• Original effective date