

MEDICAL POLICY



MEDICAL POLICY DETAILS	
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
Effective Date	01/20/11
Revised Date	11/17/11, 11/15/12, 12/19/13, 12/18/14, 11/19/15, 11/17/16, 11/16/17
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Edited Date	
Product Disclaimer	<ul style="list-style-type: none"> • <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i> • <i>If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</i> • <i>If a Medicare 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.</i>

POLICY STATEMENT

- I. Based upon our criteria and review of the peer-reviewed literature, chromosomal microarray analysis (CMA) is considered **medically necessary** 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-IV 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, and
 - B. FMR1 gene analysis (for Fragile X), when clinically indicated, is negative, and
 - C. The results for the genetic testing have the potential to impact the clinical management of the patient, and
 - D. Testing is requested after the parent(s) 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 the lack of peer-reviewed literature, chromosomal microarray analysis (CMA) is considered **investigational** in all other cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder.
- III. Based upon our criteria and review of the peer-reviewed literature, chromosomal microarray analysis (CMA) to confirm the diagnosis of a disorder or syndrome that is routinely diagnosed based on clinical evaluation alone is **not medically necessary**.
- IV. Based upon our criteria and review of the peer-reviewed literature, chromosomal microarray analysis (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 patients with a fetus with:
 - A. One or more major structural abnormalities identified on ultrasonographic examination; and
 - B. Who are undergoing invasive prenatal diagnostic testing.
- V. Based upon our criteria and review of the peer-reviewed literature, chromosomal microarray analysis (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 patients with:
 - A. A structurally normal fetus; and
 - B. Who are undergoing invasive prenatal diagnostic testing.

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Refer to Corporate Medical Policy #2.02.03 regarding Genetic Testing for Specific Diseases.

Refer to Corporate Medical Policy #4.01.03 regarding Prenatal Genetic Testing and Counseling.

Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.

Refer to Corporate Medical Policy #11.01.12 regarding Screening Tests.

POLICY GUIDELINES

- I. The American College of Medical Genetics 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 done 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 disease 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 is contract dependent. Please contact the Customer (Provider/Member) Services Department of your local plan to determine contract coverage.

DESCRIPTION

Children with signs of neurodevelopmental delays or disorders in the first few years of life may eventually be diagnosed with intellectual disability or autism syndromes, 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 Comparative Genomic Hybridization array (aCGH) has been proposed as a diagnostic tool for individuals with unexplained developmental disabilities, autism disorders or congenital anomalies

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which 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 either abnormal, benign, or as variations of unknown significance (VOUS). 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. VOUS are new chromosomal abnormalities that require additional study which includes a detailed family history and familial genetic testing to determine their significance. Currently there is a lack of standardization for CMA. There are many laboratories which perform CMA using a variety of array platforms, designs, content and internal database. A more uniform array content and a standard approach to variant interpretation as well as increased data sharing through a centralized genomic database is suggested to allow CMA to become more accepted with the potential to be used as first line testing for DD/ID, ASD and MCA.

Prenatal fetal karyotyping is a routine test initiated when the fetus is believed to be at high risk for a chromosomal abnormality as a result of a structural abnormality identified during an ultrasound exam, because of family history, or for 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

A 2009 TEC Special Report on array comparative genomic hybridization from the Blue Cross Blue Shield Association found that while aCGH technology is relatively new, the results are conceptually similar to those obtained by conventional methods, and should be evaluated as an extension of those methods. The results of neither conventional cytogenetic evaluation nor of aCGH evaluation have been systematically studied for impact on patient outcomes other than diagnostic yield, which is an intermediate outcome. Impact of testing on the kinds of outcomes that matter to the patient and family has been directly addressed in very few studies. Thus, it is not possible to draw evidence based conclusions regarding the clinical utility of aCGH genetic evaluation. The same may also be said of conventional cytogenetic evaluation.

TEC Expert consensus and clinical guidelines state that genetic information is of value because it establishes a causal explanation that is helpful to families. It is suggested that such genetic information avoids additional consultations and various types of diagnostic tests, assists with early and improved access to community services that may ameliorate or improve behavioral and cognitive outcomes, provides estimates of recurrence rates to better guide reproductive decision-making, and enables an understanding of prognosis and future needs. However, there is little evidence to support these outcomes.

TEC states that some have called for broader efforts to standardize protocols, define quality criteria for successful analysis, and develop reporting guidelines; in addition, a national multicenter trial to address accuracy, indications, and efficacy has been suggested. Currently, a consortium of scientists from academic cytogenetic laboratories have agreed to develop a uniform, evidence-based “Molecular Karyotype” and shared national database to accumulate data on pathogenic versus benign deletions and duplications in the human genome. Such cooperative efforts should lead to more comparable

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results across platforms, more complete databases to aid in individual results interpretation, more uniform reporting, and more rapid accumulation of genotype-phenotype correlation information for future reference.

The American Academy of Pediatrics (2010) included information on genomic hybridization microarray analysis in their article on clinical genetic testing for patients with autism spectrum disorders. The article stated that “specific clinical recommendations for including CMA as a first-tier test in the evaluation of patients with ASD have not kept pace with this rapidly evolving technology. Considerations for including CMA in the evaluation of children with ASD have been outlined elsewhere but have stopped short of recommending that CMA be offered as a first-tier genetic diagnostic test for ASD. On the basis of our results, genetic diagnosis will be missed in at least 5% of ASD cases without CMA, and our results suggest that CMA with whole-genome coverage should be adopted as a national standard of care for genetic testing among patients with ASDs. However the study had many limitations which included bias on selection of patients through tertiary care centers and that some of the patients may not have met full research criteria for ASD diagnosis due to the type of clinical evaluation used to determine diagnosis. In addition, the causal relationships between many of the abnormal CNVs identified in the patients with ASD and the clinical symptoms will require further study.

The American College of Medical Geneticists Practice published guidelines for array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities (2013). The guidelines state “microarray methodologies, including array comparative genomic hybridization and single-nucleotide polymorphism–detecting arrays, are accepted as an appropriate first-tier test for the evaluation of imbalances associated with intellectual disability, autism, and multiple congenital anomalies”. The utility of this technology for detection of gains and losses in patients with intellectual disabilities, autism, and/or congenital anomalies has been well documented, and CMA is now recommended as a first-tier test for these indications.

Chromosomal Microarray as a prenatal screening tool 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 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 which 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.

The American College of Obstetrics and Gynecology Committee on genetics published a statement on the use of CMA/aCGH in prenatal diagnosis (2013). The committee concluded that the use of array CGH technology in prenatal diagnosis is currently limited by several factors, including the inability to detect balanced chromosomal rearrangements, the detection of copy number variations of uncertain clinical significance, and significantly higher costs than conventional karyotype analysis. Although array CGH has distinct advantages over classic cytogenetics in certain applications, the technology is not currently a replacement for classic cytogenetics in prenatal diagnosis. The Committee recommends CMA testing for women a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis or in women 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 since 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,

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chromosomal microarray analysis on fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended. CMA is not recommended to evaluate first trimester and second-trimester pregnancy losses since data is limited. The Committee emphasizes that comprehensive patient pretest and posttest genetic counseling from qualified personnel such as a genetic counselor or geneticist regarding the benefits, limitations, and results of chromosomal microarray analysis is essential. Chromosomal microarray analysis 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.

In 2005 AHRQ published a practice parameter on evaluation of the child with global developmental delay: a report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. The committee recommended that routine cytogenetic testing (yield of 3.7%) is indicated in the evaluation of the child with developmental delay, even in the absence of dysmorphic features or clinical features suggestive of a specific syndrome. However the supporting evidence is poor (Level B recommendation; Class II and III evidence).

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 disability (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 comparative genomic hybridization [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 nonrandomized 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 we encourage researchers 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

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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	Cytogenetic 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)
81229	Cytogenetic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities.
81425	Genome (e.g., unexplained constitution or heritable disorder syndrome); sequence analysis
81426	Genome (e.g., unexplained constitution or heritable disorder syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (list separately in addition to code for primary procedure)
81427	Genome (e.g., unexplained constitution or heritable disorder syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)
81470	X-linked intellectual disability (XLID) (e.g., 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

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HCPCS Codes

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

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ICD10 Codes

Code	Description
E78.71-E78.72	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	Persistent fetal circulation
Q00.0-Q07.9	Congenital malformations of brain (code range)
Q10.0-Q18.9	Congenital malformations of eyelid (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.Q89.9	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&ContrId=298&ver=119&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AAgAAAQAAAA&