POLICY STATEMENT:

I. Based upon our criteria and review of the peer-reviewed literature, chromosomal microarray analysis (CMA) may be 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 and when the following conditions are met:
   A. The results for the genetic testing have the potential to impact the clinical management of the patient, and
   B. 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 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**.

III. 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. One or more major structural abnormalities identified on ultrasonographic examination; and
   B. Who are undergoing invasive prenatal diagnostic testing.

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. A structurally normal fetus; and
   B. Who are undergoing invasive prenatal diagnostic testing.

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. 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.
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 health plan 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.

The health plan 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 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.

A 2013 article report from The Journal of European Paediatric Neurology Society confirmed chromosomal microarray as a first-tier clinical diagnostic test for individuals with developmental delay, intellectual disability, autism spectrum disorders and dysmorphic features. Submicroscopic chromosomal rearrangements are the most common identifiable causes of intellectual disability and autism spectrum disorders associated with dysmorphic features. Chromosomal microarray (CMA) can detect copy number variants <1 Mb and identifies size and presence of known genes. The aim of the study was to demonstrate the usefulness of CMA, as a first-tier tool in detecting the etiology of unexplained intellectual disability/autism spectrum disorders (ID/ASDs) associated with dysmorphic features in a large cohort of pediatric patients. Study confirmed the value of CMA as the first-tier tool in the assessment of those conditions in the pediatric setting.

In Annals of Laboratory Medicine, the study Routine chromosomal microarray analysis is necessary in Korean patients with unexplained developmental delay/mental retardation/autism spectrum disorder (2015), the study states the “All over the world, chromosomal microarray (CMA) is now the first tier diagnostic assay for genetic testing to evaluate developmental delay (DD), mental retardation (MR), and autism spectrum disorder (ASD) with unknown etiology. The average diagnostic yield of the CMA test is known to be about 12.2%, while that of conventional G-banding karyotype is below 3%. This study aimed to assess the usefulness of CMA for the purpose of clinical diagnostic testing in the Korean population. Our findings suggest the necessity of CMA as a routine diagnostic test for unexplained DD, MR, and ASD in Korea.

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, 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, nonpaternity, 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).

**CODES:**

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81228</td>
<td>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)</td>
</tr>
<tr>
<td>81229</td>
<td>Cytogenetic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities.</td>
</tr>
<tr>
<td>81425</td>
<td>Genome (e.g., unexplained constitution or heritable disorder syndrome); sequence analysis (effective 1/1/15)</td>
</tr>
<tr>
<td>81426</td>
<td>sequence analysis, each comparator genome (e.g., parents, siblings) (list</td>
</tr>
</tbody>
</table>

*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.
separately in addition to code for primary procedure) (effective 1/1/15)
81427  re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome) (effective 1/1/15)
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 (effective 1/1/15)
81471  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 (effective 1/1/15)

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HCPCS:  S3870  Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation

ICD9:  299.00-299.01  Autistic disorder
       317-319  Mental retardation
       740.0 – 759.9  Congenital anomalies
       758.0-759.9  Chromosomal anomalies
       V28.0-V28.9  Encounter for antenatal screening of mother
       V79.2  Special screening for mental retardation
       V82.71-V82.79  Genetic screening
       V82.89  Special screening for other specified conditions
       V82.9  Special screening for other unspecified conditions

ICD10:  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)
SUBJECT: 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

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

REFERENCES:


South ST, et al. ACMG Standards and Guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: revision 2013. Genet Med 2013 Sep 26 [Epub ahead of print].


**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 no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for array comparative genomic hybridization.