MEDICAL POLICY – 12.04.59

BCBSA Ref Policy: 2.04.59
Effective Date: Oct. 1, 2017
Last Revised: Feb. 23, 2018
Replaces: 2.04.59

RELATED MEDICAL POLICIES:
12.04.102 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
12.04.116 Invasive Prenatal (Fetal) Diagnostic Testing
12.04.122 Chromosomal Microarray Analysis for the Evaluation of Pregnancy Loss
12.04.305 Preimplantation Genetic Testing in Embryos

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Chromosomal microarray analysis (CMA) is one way of testing chromosomes. It focuses on parts of a chromosome that are too small to see with a microscope. CMA can detect small areas of extra or missing parts of a chromosome. CMA can find genetic changes that are connected to developmental disabilities. This policy describes when CMA may be covered for developmental delay, or intellectual disability, autism spectrum disorder, or certain other types of health problems called congenital anomalies. This policy also discusses next-generation sequencing. This type of genetic testing can look at millions of DNA strands all at once. Next-generation sequencing produces a lot of information, but it’s unknown how all of this information relates to developmental delay. For this reason next-generation sequencing is considered unproven for developmental delay, intellectual disability, autism spectrum disorders, or congenital anomalies.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for
providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

### Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Type of Testing</th>
<th>Medical Necessity</th>
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| **Chromosomal microarray analysis (CMA)** | Chromosomal microarray analysis (CMA) may be considered medically necessary as first-line testing in the initial evaluation (see Additional Information) of individuals with any one of the following:  
  • Apparent nonsyndromic developmental delay/intellectual disability  
  OR  
  • Autism spectrum disorder  
  OR  
  • Two or more congenital anomalies not specific to a well-delineated genetic syndrome                                                                 |

Chromosomal microarray analysis (CMA) is considered investigational for the evaluation of all other conditions of delayed development, including but not limited to idiopathic growth or language delay.

<table>
<thead>
<tr>
<th>Type of Testing</th>
<th>Investigational</th>
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<tbody>
<tr>
<td><strong>Next-generation sequencing panels</strong></td>
<td>Panel testing using next-generation sequencing is considered investigational in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability, autism spectrum disorder, or congenital anomalies.</td>
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### Additional Information

- Use of CMA testing as outlined in this policy is not intended for use in the prenatal period.
- A 2013 guidelines update from American College of Medical Genetics (Schaefer et al, 2013)
Additional Information

- Recommendations from the 2010 American College of Medical Genetics guidelines (Manning et al 2010) on array-based technologies and their clinical utilization for detecting chromosomal abnormalities include the following: “Appropriate follow-up is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.”
- In some cases of CMA analysis, the laboratory performing the test confirms all reported copy number variants with an alternative technology, such as fluorescent in situ hybridization analysis.

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
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<tr>
<td>81228</td>
<td>Cytogenetic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
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<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>HCPCS</td>
<td></td>
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<tr>
<td>S3870</td>
<td>Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation</td>
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</table>

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Related Information
Definition of Terms

**Malformation:** Defects of organs or body parts due to an intrinsically abnormal developmental process. In this process, a structure is not formed, is partially formed, or is formed in an abnormal fashion.

**Major malformation:** A structural defect that has a significant effect on function or social acceptability. These often require surgical repair. Example: ventricular septal defect or a neural tube defect such as meningomyelocele or cleft lip.

**Minor malformation:** A structural abnormality that has minimal effect on function or societal acceptance. They rarely are medically significant or require surgical intervention. Examples: preauricular ear pit or partial syndactyly (fusion) of the second and third toes.

**Syndrome:** 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 and achondroplasia. However, in the very young, or in the case of syndromes with variable presentation, confident identification may be difficult without additional testing.

Consideration of Age

The age range described in this policy considers chromosomal microarray analysis testing in infants and children to be medically necessary for characteristics of developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), and/or congenital anomalies. Coverage is based on published guidelines by the American College of Medical Genetics and the American Academy of Neurology. This testing can detect genetic imbalances in infants or children with the stated characteristics and therefore provide opportunities to impact clinical management decisions.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling
will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Evidence Review

Description

Chromosomal microarray analysis (CMA) testing has been proposed for detection of genetic imbalances in infants or children with characteristics of developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), and/or congenital anomalies. CMA testing increases the diagnostic yield over karyotyping in children with the aforementioned characteristics, and CMA testing may impact clinical management decisions. Next-generation sequencing (NGS) panel testing allows for simultaneous analysis of a large number of genes and, in patients with normal CMA testing, the next-generation testing has been proposed as a way to identify single-gene causes of syndromes that have autism as a significant clinical feature.

Background

Developmental Delay/Intellectual Disability and Autism Spectrum Disorder

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.

The diagnosis of developmental delay (DD) is reserved for children younger than 5 years of age who have significant delay in 2 or more of the following developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living. Intellectual disability (ID) is a life-long disability diagnosed at or after 5 years of age when IQ testing is
considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), of the American Psychiatric Association defined patients with ID as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than 2 areas of adaptive behavior or systems of support.

According to DSM-IV, pervasive developmental disorders (PDD) encompass 5 conditions: autistic disorder, Asperger disorder, pervasive developmental disorder—not otherwise specified (PDD-NOS), childhood disintegrative disorder, and Rett syndrome. Although not mentioned in the DSM-IV, autism spectrum disorder (ASD) includes the first 3 on the list.

One of the major changes between DSM-IV and DSM-5 is the new diagnostic criteria for ASD, which include removing the term pervasive developmental disorders. Researchers found that the separate diagnoses included in PDD were not consistently applied across different clinics and treatment centers. Under DSM-5, ASD now encompasses the previous DSM-IV autistic disorder (autism), Asperger disorder, childhood disintegrative disorder, and PDD-NOS. Anyone diagnosed with one of the PDDs from DSM-IV should still meet the criteria for ASD in DSM-5.

**Congenital Anomalies**

In the United States, congenital anomalies occur in approximately 3% of all newborns and are the leading cause of neonatal morbidity and mortality. Genetic factors have been identified as an important cause of congenital anomalies. Common chromosomal aneuploidies (eg, monosomy X, trisomies 21, 18, and 13) have traditionally been diagnosed in the neonatal period using conventional karyotyping. Improved methods, such as fluorescence in situ hybridization (FISH) using chromosome or locus-specific probes, enable the diagnosis of some of the common microdeletion syndromes (eg, DiGeorge and velocardiofacial syndromes, cri-du-chat syndrome, Prader-Willi and Angelman syndromes). However, FISH is applicable only in patients with a strong clinical suspicion of a specific genetic defect, which may be difficult to detect in neonates with congenital anomalies. This is because their clinical presentation may be atypical, they may have nonspecific phenotypic features that may be shared by several different disorders, or a young patient may lack specific syndromic features that appear at a later age. An improved rate of detection of copy number variants (CNVs) has been shown with the use of array comparative genomic hybridization (aCGH).
Genetic Associations with DD/ID, ASD, and Congenital Anomalies

DD/ID and 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.

Complex autism, which comprises approximately 20% to 30% of cases of autism, is defined by the presence of dysmorphic features and/or microcephaly. Essential autism, approximately 70% to 80% of autism cases, is defined as autism in the absence of dysmorphology. Genetic causes of autism include cytogenetically visible chromosomal abnormalities (5%), single-gene disorders (5%), and CNVs (10%-20%). Single-nucleotide polymorphism (SNP) microarrays to perform high-resolution linkage analysis have revealed suggestive regions on certain chromosomes not previously associated with autism. To date, the SNP findings in autism seem consistent with other complex diseases, in which common variation has modest effect size (odds ratio, <2), requiring large samples for robust detection. This diagnostic challenge makes it unlikely that individual single nucleotide variants (SNVs) will have high predictive value.\(^2\)

Guidelines for patients with ID/DD, ASD, and/or congenital anomalies, such as those published by the American Academy of Pediatrics\(^3\) (AAP) and the American Academy of Neurology (AAN) with the Child Neurology Society (CNS), have recommended cytogenetic evaluation to look for certain kinds of chromosomal abnormalities that may be causally related to their condition\(^4\). The joint AAN and CNS guidelines have noted that only occasionally will an etiologic diagnosis lead to specific therapy that improves outcomes, but suggest the more immediate and general clinical benefits of achieving a specific genetic diagnosis from the clinical viewpoint, as follows\(^4\):

- “limit further diagnostic testing”
- “improve understanding of treatment and prognosis”
- “anticipate and manage associated medical and behavioral comorbidities”
- “allow for counseling regarding risk of recurrence, and prevent recurrence through screening for carriers and prenatal testing.”
The AAP and the joint AAN and CNS guidelines have also emphasized the importance of early diagnosis and intervention in an attempt to ameliorate or improve behavioral and cognitive outcomes over time.

At present, a relatively small body of literature has addressed the use of CMA or other genetic testing for predicting disease phenotype or severity. This is not yet a major clinical use of testing and is not a focus in this review.

**Testing to Determine Genetic Etiology**

Most commonly, genetic abnormalities associated with neurodevelopmental disorders are deletions and duplications of large segments of genomic material, called copy number variants (CNVs). For many well-described syndromes, the type and location of the chromosomal abnormality have been established with the study of a large number of cases and constitute a genetic diagnosis; for others, only a small number of patients with similar abnormalities may exist to support a genotype-phenotype correlation. Finally, for some patients, cytogenetic analysis will discover entirely new chromosomal abnormalities that will require additional study to determine their clinical significance.

Conventional methods of cytogenetic analysis, including karyotyping (eg, G-banded) and FISH, have relatively low resolution and a low diagnostic yield (ie, proportion of tested patients found to have clinically relevant genomic abnormalities), leaving most cases without identification of a chromosomal abnormality associated with the child’s condition. CMA testing is a newer cytogenetic analysis method that increases the chromosomal resolution for detection of CNVs, and, as a result, increases the genomic detail beyond that of conventional methods. CMA results are clinically informative in the same way as results derived from conventional methods, and thus CMA represents an extension of standard methods with increased resolution.

**CMA Testing**

The term CMA collectively describes two different array platforms: aCGH and SNP arrays. Both types of arrays can identify loss or gain of DNA (microdeletions or microduplications, respectively), known as CNVs. CMA testing can identify genomic abnormalities associated with a wide range of developmental disabilities, including cognitive impairment, behavioral abnormalities, and congenital abnormalities. CMA testing can detect CNVs, and the frequency of
disease-causing CNVs is highest (20%-25%) in children with moderate-to-severe intellectual disability accompanied by malformations or dysmorphic features. Disease-causing CNVs have been identified in 5% to 10% of cases of autism, being more frequent in severe phenotypes.⁶,⁷

**Array Comparative Genomic Hybridization and Single-Nucleotide Polymorphism**

The aCGH technique uses a DNA sample from the patient and a DNA sample from a normal control. Each is labeled with 1 color of fluorescent dye (red or green) and the labeled samples are mixed and hybridized to thousands of cloned or synthesized reference (normal) DNA fragments of known genomic locus immobilized on a glass slide (microarray) to conduct thousands of comparative reactions at the same time. CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. If the patient sequence is missing part of the normal sequence (deletion) or has the normal sequence plus additional genomic material within that genomic location (eg, a duplication of the same sequence), the sequence imbalance is detected as a difference in fluorescence intensity. For this reason, aCGH cannot detect balanced CNVs (equal exchange of material between chromosomes) or sequence inversions (same sequence is present in reverse base pair order) because the fluorescence intensity would not change.

SNVs are the most common genetic variation among people and occur normally throughout the DNA. Each SNV represents a difference in a single nucleotide. On average, a SNV occurs every 300 nucleotides. SNVs can act as “biological markers,” in that they may identify genes associated with disease. Most SNVs have no deleterious effect, but may predict an individual's response to certain drugs, susceptibility to environmental factors, and the risk of developing certain diseases. SNVs may also indicate inheritance of disease genes within families.

Like aCGH, SNP arrays also detect CNVs, although the resolution provided by aCGH is better than that with SNP arrays, and, therefore, SNP arrays are limited in the detection of single exon CNVs. In addition, aCGH has better signal-to-background characteristics than SNP arrays. In contrast to aCGH, SNP arrays will also identify long stretches of DNA homozygosity, which may suggest uniparental disomy (UPD) or consanguinity. UPD occurs when someone inherits 2 copies of a chromosome from 1 parent and no copies from the other parent. UPD can lead to syndromes such as Angelman and Prader-Willi. SNP arrays can also detect triploidy, which cannot be detected by aCGH arrays.

A portion of the increased diagnostic yield from CMA over karyotyping comes from the discovery that some chromosomal rearrangements that appear balanced (and therefore not
pathogenic) by G-banded karyotype analysis are found to have small imbalances with greater resolution. It has been estimated that 40% of apparently balanced de novo or inherited translocations with abnormal phenotype are associated with cryptic deletion if analyzed by CMA testing.

The various types of microarrays can differ by construction; earliest versions used DNA fragments cloned from bacterial artificial chromosomes. They have been largely replaced by oligonucleotide (oligo; short, synthesized DNA) arrays, which offer better reproducibility. Oligo/SNP hybrid arrays have been constructed to merge the advantages of each.

Microarrays may be prepared by the laboratory using the technology or, more commonly, by commercial manufacturers, and sold to laboratories that must qualify and validate the product for use in their assay, in conjunction with computerized software for interpretation. The proliferation of in-house developed and commercially available platforms prompted the American College of Medical Genetics (ACMG) to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting.8

Copy Number Variants

Targeted CMA provides high-resolution coverage of the genome primarily in areas containing known, clinically significant CNVs. The ACMG guideline for designing microarrays recommends probe enrichment in clinically significant areas of the genome to maximize detection of known abnormalities – however, they also recommend against the use of targeted arrays in the postnatal setting. Rather, a broad genomic screen is recommended to identify atypical, complex, or completely new rearrangements, and to delineate breakpoints accurately.

Whole-genome CMA has allowed the characterization of several new genetic syndromes, with other potential candidates currently under study. However, the whole-genome arrays also have the disadvantage of potentially high numbers of apparent false-positive results, because benign CNVs are also found in phenotypically normal populations. Both benign and pathogenic CNVs are continuously cataloged and, to some extent, made available in public reference databases to aid in clinical interpretation. Additionally, some new CNVs are neither known to be benign nor causal. These CNVs may require detailed family history and family genetic testing to determine clinical significance and/or may require confirmation by subsequent accumulation of similar cases and so, for a time, may be considered a CNV of undetermined significance (some may eventually be confirmed true positives or causal, others false positives or benign).
To determine clinical relevance (consistent association with a disease) of CNV findings, the following actions are taken:

- CNVs are confirmed by another method (e.g., FISH, multiplex ligation-dependent probe amplification, polymerase chain reaction).

- CNVs detected are checked against public databases and, if available, against private databases maintained by the laboratory. Known pathogenic CNVs associated with the same or similar phenotype as the patient are assumed to explain the etiology of the case; known benign CNVs are assumed to be nonpathogenic.\(^{9-11}\)

- A pathogenic etiology is additionally supported when a CNV includes a gene known to cause the phenotype when inactivated (microdeletion) or overexpressed (microduplication)\(^ {10} \)

- The laboratory may establish a size cutoff; potentially pathogenic CNVs are likely to be larger than benign polymorphic CNVs; cutoffs for CNVs not previously reported typically range from 300 kilobase (kb) pairs to 1 megabase pairs (Mb)\(^ {11-14}\).

- Parental studies are indicated when CNVs of appropriate size are detected and not found in available databases; CNVs inherited from a clinically normal parent are assumed to be benign polymorphisms whereas those appearing de novo are likely pathogenic; etiology may become more certain as other similar cases accrue.\(^ {9,15}\)

ACMG has also published guidelines for the interpretation and reporting of CNVs in the postnatal setting in order to promote consistency among laboratories and CMA results.\(^ {16}\) Three categories of clinical significance are recommended for reporting: pathogenic, benign, and uncertain clinical significance.

In 2008, the International Standards for Cytogenomic Arrays (ISCA) Consortium was organized (available at: www.clinicalgenome.org/). It has established a public database containing deidentified whole-genome microarray data from a subset of the ISCA Consortium member clinical diagnostic laboratories. Array analysis was carried out on subjects with phenotypes including DD/ID and ASD. As of August 2017, there were nearly 54,000 subjects with individual-level data in the database.\(^ {17}\) Additional members are planning to contribute data; participating members use an opt-out, rather than an opt-in approach that was approved by the National Institutes of Health (NIH) and participating center institutional review boards. The database is held at National Center for Biotechnology Information/NIH and curated by a committee of clinical genetics laboratory experts. In 2011, Kaminsky et al used data from the ISCA consortium, including 15,749 cases and 10,118 published controls available at the time of analysis, to identify...
the functional significance of 14 rare CNVs in intellectual and developmental disabilities, and to describe a methodology for assessing for pathologic CNVs. In the Kaminsky study, the frequency of pathogenic CNVs was 17.1%.

**Next-Generation Sequencing**

Next-generation sequencing (NGS) has been proposed to detect single-gene causes of autism and possibly identify a syndrome that involves autism in patients with normal array-based testing. NGS involves the sequencing of millions of fragments of genetic material in a massively parallel fashion. NGS can be performed on segments of genetic material of a variety of sizes – from the entire genome (whole-genome sequencing) to small subsets of genes (targeted sequencing). NGS allows the detection of SNVs, CNVs, and insertions and deletions. With higher resolution comes higher likelihood of detection of variants of uncertain clinical significance.

**Summary of Evidence**

For individuals who have developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive chromosomal microarray (CMA) testing, the evidence includes primarily case series. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. The available evidence supports test accuracy and validity. Although systematic studies of the impact of CMA on patient outcomes are lacking, the improvement in diagnostic yield over karyotyping has been well demonstrated. Direct evidence of improved outcomes with CMA compared with karyotyping is lacking. However, for at least a subset of the disorders potentially diagnosed with CMA in this patient population, there are well-defined and accepted management steps associated with positive test results. Further, there is evidence of changes in reproductive decision making as a result of positive test results. The information derived from CMA testing can accomplish the following: it could end a long diagnostic odyssey; reduce morbidity for certain conditions by initiating surveillance or management of associated comorbidities; or it could potentially impact future reproductive decision making for parents. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have DD/ID, ASD, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive next-generation sequencing (NGS) panel testing, the
evidence includes primarily case series. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. The rates of variants of uncertain significance associated with NGS panel testing in this previously described patient population are not well-characterized. The yield of testing and likelihood of an uncertain result is variable, based on gene panel, gene tested, and patient population: Additionally, there are real risks of uninterpretable and incidental results. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing And Unpublished Clinical Trials**

A search of ClinicalTrials.gov in July 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

**Clinical Input From Physician Specialty Societies And Academic Medical Centers**

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

**2011 Input**

In response to requests, clinical input was received from 2 physician specialty societies and 2 academic medical centers while this policy was under review in 2011. Clinical input focused on the clinical utility of chromosomal microarray (CMA) testing. As in 2010, reviewers supported the use of CMA testing for the diagnosis in patients with developmental delay and autism spectrum disorder. Reviewers acknowledged the lack of evidence in the literature on clinical utility, such as the lack of literature demonstrating improved outcomes as a result of testing. Reviewers cited multiple anecdotal and theoretical clinical situations in which management changes resulted from results of CMA testing. Reviewers also agreed that this test was widely used in standard care with the support of the genetics community.
2010 Input

In response to requests, clinical input was received through 3 physician specialty societies and 2 academic medical centers while this policy was under review in early 2010. Those providing input supported use of targeted CMA testing in children with developmental delay, intellectual disability, and autism spectrum disorder in several situations. There was less support for whole-genome array testing. However, targeted array testing is now primarily available for prenatal analysis, whereas whole-genome arrays are recommended as standard.

Practice Guidelines and Position Statements

American Academy of Pediatrics

In 2014, the American Academy of Pediatrics issued a clinical report on the optimal medical genetics evaluation of a child with or global developmental delays (GDD) or intellectual disability (ID).3 Regarding chromosomal microarray (CMA) testing, this report stated:

CMA now should be considered a first tier diagnostic test in all children with GDD/ID for whom the causal diagnosis is not known.... CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies.

American Academy of Child and Adolescent Psychiatry

In 2014, the American Academy of Child and Adolescent Psychiatry updated its guidelines on the assessment and treatment of children and adolescents with autism spectrum disorder (ASD).42 The Academy recommended that “all children with ASD should have a medical assessment, which typically includes physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis, and genetic testing, which may include G-banded karyotype, fragile X testing, or chromosomal microarray.”
American Academy of Neurology and Child Neurology Society

In 2011, the American Academy of Neurology and the Child Neurology Society updated their
guidelines on the evaluation of unexplained global DD/ID with information on genetic and
metabolic (biochemical) testing to accommodate advances in the field. The guidelines conclude
that CMA testing has the highest diagnostic yield in children with DD/ID, 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.”

American College of Medical Genetics

The American College of Medical Genetics (ACMG) published guidelines on array-based
technologies and their clinical utilization for detecting chromosomal abnormalities in 2010. CMA
testing for copy number variants (CNVs) was recommended as a first-line test in the initial
postnatal evaluation of individuals with the following:

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

B. Apparently non-syndromic DD/ID

C. ASD

Additional ACMG guidelines have addressed the design and performance expectations for
clinical microarrays and associated software and for the interpretation and reporting of CNVs,
both intended for the postnatal setting. A 2013 update included recommendations for validation
of microarray methodologies for both prenatal and postnatal specimens.

A 2013 guideline revision from ACMG stated that a stepwise or tiered approach to the clinical
genetic diagnostic evaluation of ASD is recommended, with the recommendation being for first-
tier to include fragile X syndrome and CMA, and second tier to include MECP2 and PTEN
testing. The guideline stated that:

This approach will evolve with continued advancements in diagnostic testing and improved
understanding of the ASD phenotype. Multiple additional conditions have been reported in
association with an ASD phenotype, but none of these has been evaluated in a large
prospective cohort. Therefore, a future third tier of evaluation is a distinct possibility. Further
studies would be needed to elevate the evidence to the point of recommended testing. Alternatively, advances in technology may permit bundling of individual tests into an extended, more readily accessible, and less expensive platform. The accumulating evidence using next-generation sequencing (third tier testing) will increase the diagnostic yield even more over the next few years.

**International Standard Cytogenomic Array Consortium**

The International Standard Cytogenomic Array Consortium published a Consensus Statement in 2010 in which it recommended offering CMA as the first-tier genetic test, in place of G-banded karyotype, for patients with unexplained DD/ID, ASD, or multiple congenital anomalies (MCA). “Except in special cases, such as those involving family history of multiple miscarriages, a karyotype is not cost effective in a child with DD/ID, ASD, or MCA and a negative array study. CMA testing is not inexpensive, but the cost is less than the cost of a G-banded karyotype plus a customized fluorescent in situ hybridization (FISH) test such as subtelomeric FISH, and the yield is greater.”

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Lab tests for CMA and NGS are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In July 2010, FDA indicated that it would require microarray manufacturers to seek clearance to sell their products for use in clinical cytogenetics.
CMA Testing

CMA testing is commercially available through many laboratories and includes targeted and whole-genome arrays, with or without SNP microarray analysis.

On January 17, 2014, the Affymetrix CytoScan® Dx Assay (Thermo Fisher Scientific, Waltham, MA) has been cleared by the U.S. Food and Drug Administration (FDA) through the de novo 510(k) process. FDA’s review of the CytoScan® Dx Assay included an analytic evaluation of the test’s ability to detect accurately numerous chromosomal variations of different types, sizes, and genome locations compared with several analytically validated test methods. FDA found that the CytoScan® Dx Assay could detect copy number variations (CNVs) across the genome and adequately detect CNVs in regions of the genome associated with ID/DD. Reproducibility decreased with the CNV gain or loss size, particularly when less than approximately 400 kb (generally recommended as the lower reporting limit). As of July 2017, Affymetrix™ has reported 2.69 million markers for copy number, 750,000 biallelic probes, and 1.9 million polymorphic probes (Affymetrix™ was acquired by Thermo Fisher Scientific in 2016). FDA product code: PFX.

FirstStep Dx PLUS® (Lineagen, Salt Lake City, UT) uses Lineagen’s custom-designed microarray platform manufactured by Affymetrix. As of July 2017, this microarray consists of a 2.8 million probe microarray for the detection of CNVs associated with neurodevelopmental disorders. The array includes probes that come standard on the Affymetrix CytoScan HD® microarray, with an additional 88,435 custom probes designed by Lineagen.

Ambry Genetics (Aliso Viejo, CA) offers multiple tests (CMA and NGS) that are designed for ASD and neurodevelopmental disorders. As of July 2017, the CMA offered by Ambry Genetics includes over 2.6 million probes for copy number and 750,000 SNP probes. The expanded NGS panel for neurodevelopmental disorders includes assesses 196 genes.

LabCorp (Burlington, NC) offers the Reveal® SNP Microarray-Pediatric for individuals with nonsyndromic congenital anomalies, dysmorphic features, DD/ID, and/or ASD. The Reveal® microarray has 2695 million probes as of July 2017.
Next-Generation Sequencing

A variety of commercial and academic laboratories offer NGS panels designed for the evaluation of ASD, DD/ID, and congenital anomalies, which vary in terms of the numbers of and specific genes tested.

Emory Genetics Laboratory (North Decatur, GA) offers an NGS ASD panel of genes targeting genetic syndromes that include autism or autistic features.

Greenwood Genetics Center (Greenwood, SC) offers an NGS panel for syndromic autism that includes 83 genes.

References


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<tr>
<th>Date</th>
<th>Comments</th>
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<tbody>
<tr>
<td>09/14/10</td>
<td>Add to Pathology/Laboratory section. - New Policy. Published on 2/1/11 following 90-day hold for provider notification.</td>
</tr>
<tr>
<td>02/14/12</td>
<td>Replace Policy – Policy updated with literature search; references 1, 2, 6, 10, 19, 20, 24, 29, 30, 33, 35 added. Term “array comparative genomic hybridization (aCGH)” changed to “chromosomal microarray (CMA) analysis” in title, policy statements, and text. Policy statements changed to medically necessary for infants and children with developmental delay, intellectual disability, or autism spectrum disorder under certain conditions; investigational for all other indications. Modified statement about specific types of genetic counselors to a more general description and the term “mental retardation” changed to “intellectual disability” throughout and in the title.</td>
</tr>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.59 (previously 2.04.59) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>08/15/12</td>
<td>Update Related Policies – Add 12.04.83.</td>
</tr>
<tr>
<td>01/11/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
</tr>
<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>09/20/13</td>
<td>Update Related Policies. Add 12.04.305.</td>
</tr>
<tr>
<td>12/09/13</td>
<td>Replace policy. Policy updated with literature search; references 11, 35, 37, 38 and 40 added. No change in policy statements. CPT codes 81200-81479, 81599, and 88384-88386 removed as they are not specific to this policy; 83890-83913 removed because they are now deleted.</td>
</tr>
<tr>
<td>12/08/14</td>
<td>Annual Review. Policy statement added that NGS panel testing is considered investigational in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder. Title changed to include NGS. No change to postnatal policy statements. Prenatal testing removed from this policy and added to new policy on Invasive Prenatal (Fetal) Diagnostic Testing. Remove ICD-9 and ICD-10 diagnosis codes; these are not utilized in adjudication of the policy.</td>
</tr>
<tr>
<td>03/24/15</td>
<td>Update Related Policies. Change title to 12.04.122.</td>
</tr>
<tr>
<td>10/13/15</td>
<td>Annual Review. Policy updated with literature review through June 15, 2015. Policy statements changed that CMA may be considered medically necessary as first line testing for apparently nonsyndromic developmental delay/intellectual disability, autism spectrum disorder, and multiple (two or more) anomalies not specific to a well-delineated genetic syndrome. Investigational statement regarding CMA added as a local plan variance. Definitions added to Guidelines. Reference 33 was added.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>08/01/16</td>
<td>Interim Review, approved July 12, 2016. 12.04.116 Invasive Prenatal (Fetal) Diagnostic Testing added to Related Policies to assist in distinction between fetal CMA testing (12.04.116) and infant/child CMA testing (12.04.59).</td>
</tr>
<tr>
<td>07/07/17</td>
<td>Policy moved into new format; no change to policy statements.</td>
</tr>
<tr>
<td>01/23/18</td>
<td>Coding update, added CPT codes 81258, 81259, and 81269 (new codes effective 1/1/18).</td>
</tr>
<tr>
<td>02/23/18</td>
<td>Coding update, removed CPT codes 81258, 81259, and 81269 from the policy as they were moved to a more appropriate policy.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

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Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at:
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at:

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Oromo (Cushite):
Lakkoofsa biibliiwa 800-722-1471 (TTY: 800-842-5357) ti biibliiwa.

Français (French):
 Appelez le 800-722-1471 (TTY: 800-842-5357).

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