**MEDICAL POLICY – 12.04.59**

**Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies**

BCBSA Ref Policy: 2.04.59

**Effective Date:** Dec. 1, 2018

**Last Revised:** Nov. 21, 2018

**Replaces:** 2.04.59

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

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**Introduction**

Chromosomal microarray (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, 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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</thead>
</table>
| Chromosomal microarray analysis (CMA) | Chromosomal microarray analysis 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>
</tr>
</thead>
<tbody>
<tr>
<td>Next-generation sequencing panels</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>
</tr>
</tbody>
</table>

### Additional Information

- Use of CMA testing as outlined in this policy is not intended for use in the prenatal period.
- A guidelines update from American College of Medical Genetics (Schaefer et al, 2013) stated that a stepwise (or tiered) approach to the clinical genetic diagnostic evaluation of autism spectrum disorder is recommended, with the recommendation being for the first tier to include fragile X syndrome and chromosomal microarray (CMA) testing.
- Recommendations from the American College of Medical Genetics guidelines (Manning et al
**Additional Information**

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>
<td></td>
</tr>
<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>
</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>HCPCS</td>
<td></td>
</tr>
<tr>
<td>S3870</td>
<td>Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

**Related Information**

**Definition of Terms**

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

**Minor malformation:** A structural abnormality that has minimal effect on function or societal acceptance. Minor malformations are medically significant or require surgical intervention. Examples include 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.

**Genetics Nomenclature Update**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

**Table 1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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.
Description

Chromosomal microarray (CMA) testing has been proposed for detection of genetic imbalances in infants or children with characteristics of developmental delay/intellectual disability, autism spectrum disorder, 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 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

Developmental delay (DD) is diagnosed in children 5 years or younger who show a significant delay in 2 or more developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living.\(^1\) DD can precede the development of intellectual disability (ID) as the child ages.\(^2\)

ID is manifest by significant limitations in intellectual functioning and adaptive behavior. It is diagnosed at or after age 5 (when intelligence testing is considered valid and reliable) but prior to age 18 and is lifelong. The *Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition (DSM-5)* defines ID as occurring during the developmental period and involving impairments of general mental abilities (eg, IQ <70 or 75) that impact adaptive functioning in the conceptual, social, and practical domains.\(^3\)

Prevalence estimates of DD and ID range from 1% to 3%.\(^4\) Both are influenced by genetic, environmental, infectious, and perinatal factors. Approximately 450 genes have been causally related to ID; most genes (~90%) are associated with syndromes.\(^5\) Inheritance of ID can be autosomal-dominant, recessive, or X-linked; and most nonsyndromic genes are located on the X chromosome. Prior to the advent of whole-exome and genome sequencing, Willemsen and Kleefstra (2014) concluded that 20% to 40% of ID cases could be attributed to a genetic variant.\(^6\)
With the use of whole-genome sequencing, they estimated almost 60% of cases have an identifiable genetic etiology.

Congenital anomalies are frequently present in children with DD and ID. In addition, a suspected etiology can often be established from history and physical examination (in skilled specialists as much as 20% to 40% of cases) without genetic testing. The recommended approach to evaluation in DD/ID begins with a 3-generation family history and physical (including neurologic) exam. Subsequent testing is used to confirm a suspected diagnosis (eg, targeted fluorescent in situ hybridization [FISH] testing for DiGeorge or cri-du-chat syndromes). If no diagnosis is suspected, fragile X syndrome testing, metabolic testing for inborn errors of metabolism, and chromosomal microarray (CMA) testing (without karyotyping) are recommended—regardless of the presence or absence of dysmorphologic features or congenital anomalies.

**Autism Spectrum Disorder**

DSM-5 defines autism spectrum disorder (ASD) as the presence of:

- Persistent deficits in social communication and social interaction across multiple contexts,
- Restricted, repetitive patterns of behavior, interests, or activities,
- Symptoms must be present in the early developmental period (typically recognized in the first 2 years of life), and
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

In 2010, the estimated prevalence of ASD among 8-year-olds was 14.7 per 1000, or 1 in 68. ASD is 4 to 5 times more common in boys than girls, and white children are more often identified with ASD than black or Hispanic children. An accurate diagnosis can generally be made by age 2. The evaluation includes developmental screening and diagnostic evaluation (ie, hearing, vision, neurologic, laboratory testing for metabolic disorders, and genetic testing).

A large body of evidence supports a genetic etiology in ASD. Twin studies estimate heritability between 60% and 90%. A family with an affected child has a 13% to 19% risk for recurrence in subsequent children. Based on Swedish genetic studies, Gaugler et al (2014) concluded that “the bulk of autism arises from genetic variation” (as opposed to environmental causes). Still, although genetic determinants can be heritable, most appear to arise de novo.
For these reasons, a child with ASD is often evaluated with genetic testing. Testing may be targeted when a child has a recognizable syndrome such as those shown in Table 3. Alternatively, high-resolution cytogenetic analysis evaluating multiple genes—the focus of this evidence review—is used.


<table>
<thead>
<tr>
<th>Gene (Syndrome)</th>
<th>Patient Selection</th>
<th>Yield, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMR1 (fragile X)</td>
<td>Unselected autism</td>
<td>3-10</td>
<td></td>
</tr>
<tr>
<td>MECP2 (Rett)</td>
<td>Females with nonsyndromic autism, intellectual disability, and cerebral palsy</td>
<td>3-13</td>
<td>Schaefer and Mendelsohn (2008)12</td>
</tr>
</tbody>
</table>

Table 3. Examples of Specific Genes Associated With Disorders That Include Autistic Behaviors

**Diagnostic Testing**

**Karyotyping and FISH**

The goal of a cytogenetic evaluation is to identify chromosomal imbalances that cause a disorder. The most common imbalances are copy number variants (CNVs) or deletions and duplications of large segments of genomic material. CNVs are common in DD/ID and ASD but more often reflect normal genetic variation. However, de novo CNVs are observed about 4 times more frequently in children with ASD than in normal individuals. Less frequently, other abnormalities such as balanced translocations (ie, exchanges of equally sized DNA loci between chromosomes) may be pathogenic. For many well-described syndromes, the type and location of the associated chromosomal abnormality have been established by studying large patient samples. For others, few patients with similar abnormalities may have been evaluated to establish genotype-phenotype correlation. Finally, in some patients, cytogenetic analysis will discover chromosomal abnormalities that require study to determine their significance.

Prior to the advent of CMAs, the initial step in cytogenetic analysis was G-banded karyotyping, which evaluates all chromosomes. High-resolution G-banding can detect changes as small as 3 to 5 megabases in size, although standard G-banding evaluates more than 10 megabases changes. In children with DD/ID, a review by Stankiewicz and Beaudet (2007) found G-banded
karyotyping diagnostic in approximately 3% to 5%. In ASD, high-resolution karyotyping appears to identify abnormalities in up to 5% of cases.

In contrast, molecular cytogenetic techniques can detect small submicroscopic chromosomal alterations. FISH, a targeted approach, is used to identify specific chromosomal abnormalities associated with suspected diagnoses such as DiGeorge syndrome. Prior to CMAs, FISH was also used to screen the rearrangement-prone subtelomeric regions. Subtelomeric FISH was found to identify abnormalities in children with DD and ID, diagnostic in approximately 5% to 6% of those with negative karyotypes, but uncommonly in ASD.

**Chromosomal Microarrays**

Two types of CMAs are considered here: array comparative genomic hybridization (aCGH) and single nucleotide variants (SNV) arrays. The aCGH approach uses DNA samples from a patient and a normal control. Each is labeled with distinct fluorescent dyes (red or green). The labeled samples are then 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 simultaneously. 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 (a deletion) or has the normal sequence plus additional genomic material within that genomic location (eg, a duplication), the sequence imbalance is detected as a difference in fluorescence intensity (Korf and Rehm [2013] offer an illustrative graphic). For this reason, aCGH cannot detect balanced chromosomal translations (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. A portion of the increased diagnostic yield from CMA over karyotyping comes from the discovery that 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.

Like aCGH, SNV arrays detect CNVs. In an SNV array, the 2 alleles for genes of interest are tagged with different florescent dyes. Comparative florescence intensity will be increased when there are duplications and diminished with deletions. The resolution provided by aCGH is higher than with SNV arrays. In addition, aCGH has better signal-to-background characteristics than SNV arrays. In contrast to aCGH, SNV arrays will also identify long stretches of DNA homozygosity, which may suggest uniparental disomy or consanguinity. Uniparental disomy
occurs when a child inherits 2 copies of a chromosome from 1 parent and no copies from the other parent. Uniparental disomy can lead to syndromes such as Angelman and Prader-Willi.

Table 4 summarizes the cytogenetic tests used to evaluate children with DD/ID and autism. The table emphasizes the large difference in resolution between karyotyping and CMA.

**Table 4. Resolution and Analysis Comparison of FISH, Karyotyping, and CMA Analysis**

<table>
<thead>
<tr>
<th>Test</th>
<th>Resolution in Kilobases&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotyping</td>
<td>3000-5000 kb</td>
<td>Genome-wide</td>
</tr>
<tr>
<td>CMA</td>
<td>≈50 kb</td>
<td>Genome-wide</td>
</tr>
<tr>
<td>FISH</td>
<td>≈500 to 1000 kb (depending on probe)</td>
<td>Targeted</td>
</tr>
</tbody>
</table>

CMA: chromosomal microarray; FISH: fluorescent in situ hybridization; kb: kilobases.
<sup>a</sup> One kb = 1000 bases, 1000 kb = 1 Mb.

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 laboratory-developed and commercially available platforms prompted the American College of Medical Genetics to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting.<sup>20</sup>

**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.
Genetic Associations with DD/ID and ASD

For common phenotypes and syndromes, the pathogenicity of CNVs may be supported by considerable evidence; for uncommon phenotypes and uncommon CNVs determining pathogenicity requires a systematic evaluation that includes parental studies, examining databases for reported associations, and considering the molecular consequences of the identified variant. Parental studies (eg, “trio” testing of affected child, father, and mother) can identify an inherited CNV from an unaffected parent and therefore considered benign. A variety of databases index the clinical implications of CNVs and their associations with a particular phenotype. CNVs are continuously cataloged and, with growth in CMA testing and improved resolution, databases have become increasingly extensive (eg, DECIPHER [https://decipher.sanger.ac.uk], ClinVar [http://www.ncbi.nlm.nih.gov/clinvar/]). For uncommon CNVs, in addition to reports of CNV-phenotype associations, the location and size of the CNV can offer clues to pathogenicity; larger CNVs are more often pathogenic and the role of affected genes in brain circuitry and effect of CNV on gene expression can implicate pathogenicity. Although uncommon, an observed phenotype can result from unmasking a mutated recessive allele on the unaffected (non-CN) chromosome. Other considerations when determining pathogenicity include CNV dosage, X linkage, number of reports in the literature of an association between CNV and phenotype, and findings in “normal” individuals.

The American College of Medical Genetics has published guidelines for evaluating, interpreting, and reporting pathogenicity reflecting these principles. The recommended categories of clinical significance for reporting are pathogenic, uncertain clinical significance (likely pathogenic, likely benign, or no subclassification), or benign. The International Standards for Cytogenomic Arrays Consortium more recently proposed “an evidence-based approach to guide the development of content on chromosomal microarrays and to support interpretation of clinically significant copy number variation.” The proposal defined levels of evidence describe how well or how poorly detected variants or CNVs correlate with phenotype.

Summary of Evidence

For individuals who have DD/ID, ASD, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive CMA testing, the evidence includes primarily case series. Relevant outcomes are test validity, changes in reproductive decision making, morbid events, and resource utilization. The available evidence supports test 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 also lacking. However, for at least a subset of the disorders potentially diagnosed with CMA testing 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/management of associated comorbidities, or impact future reproductive decision making for parents. The evidence is sufficient to determine 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 panel testing, the evidence includes primarily case series. Relevant outcomes are test validity, changes in reproductive decision making, morbidity, and resource utilization. The diagnostic yield associated with next-generation sequencing panel testing in this patient population is not well-characterized. The testing yield and likelihood of an uncertain result are variable, based on the gene panel, gene tested, and patient population; additionally, there are 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 September 2018 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 collaborate with and make recommendations during this process, through the provision of appropriate reviewers, 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. 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 were made based on the 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 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

The American Academy of Pediatrics (2014) issued a clinical report on the optimal medical genetics evaluation of a child with developmental delays (DD) or intellectual disability (ID). 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

The American Academy of Child and Adolescent Psychiatry (2014) updated its guidelines on the assessment and treatment of children and adolescents with autism spectrum disorder (ASD)\textsuperscript{110}. 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

The American Academy of Neurology and the Child Neurology Society (2011) updated their guidelines on the evaluation of unexplained DD and ID with information on genetic and metabolic (biochemical) testing to accommodate advances in the field.\textsuperscript{4} 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, 2010) published guidelines on array-based technologies and their clinical utilization for detecting chromosomal abnormalities in 2010.\textsuperscript{111} CMA testing for copy number variants 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

Other ACMG guidelines have addressed the design and performance expectations for clinical microarrays and associated software\textsuperscript{20} and for the interpretation and reporting of copy number variants,\textsuperscript{23} both intended for the postnatal setting. A 2013 update included recommendations for validation of microarray methodologies for both prenatal and postnatal specimens.\textsuperscript{112}
The guideline revisions from ACMG (2013) stated that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of ASD is recommended, with the first-tier including fragile X syndrome and CMA, and the second tier MECP2 and PTEN testing.\textsuperscript{113} The guidelines 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.

**Medicare National Coverage**

There is no national coverage determination.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act. Lab tests for CMA and NGS are available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments 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 2010, the 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.
In January 2014, the Affymetrix CytoScan® Dx Assay (Thermo Fisher Scientific) was cleared by the FDA through the de novo 510(k) process. The FDA’s review of the CytoScan® Dx Assay included an analytic evaluation of the test’s ability to accurately detect numerous chromosomal variations of different types, sizes, and genome locations compared with several analytically validated test methods. The FDA found that the CytoScan® Dx Assay could detect 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.

FirstStepDx PLUS® (Lineagen) 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 offers multiple tests (CMA and NGS) designed for diagnosing 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 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 offers an NGS ASD panel of genes targeting genetic syndromes that include autism or autistic features.

Greenwood Genetics Center offers an NGS panel for syndromic autism that includes 83 genes.
References


17. Moeschler JB. Medical genetics diagnostic evaluation of the child with global developmental delay or intellectual disability. Curr Opin Neurol. Apr 2008;21(2):117-122. PMID 18317267


<table>
<thead>
<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. Removed related policy 12.04.83 – it was archived.</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 customer service representative to determine whether there are any benefit limitations applicable to this service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

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.


Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action because of race, color, national origin, age, disability or sex. Premera does not discriminate on the basis of race, color, national origin, age, disability or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb baa twj koj daitw thov kev pab los yoy koj chov kev pab cuam los ntawn Premera Blue Cross. Tej zaum muaj cov hnb tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj koy juav tau ua qee yam uas peb koj uas tis pub dhaav cov cajy nyong uas teev tse Ag rau hauv daim ntaww no mas koj thaj yuav taub baiz kev pab cuam kho moh los yoy kev pab them tej ni qk hmoi ntaww. Koj muaj cai kom laww muab cov ntsiab lus uas t leading muab sau uak jo houk lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Illok (Ilocano):
Daytoy a Pakdaa ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaa mabalini nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyon uyo coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pelta iti daytoy a pakdaa. Mabalini nga adda rumbeng nga aramidenyo nga adda sakyb dagiti partikular a naituding nga aildaw tapno mapagatan.edu ti coverage ti salun-ayno wi nga tulong kadagit gastos. Adda karbenganyo a magangita iti daytoy nga impormasion ken tulong iti bukodyo a pagasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Chinese (Chinese):
本通知有重要的讯息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保護或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).
Japanese (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている情報がある場合、健康保険や無料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。この通知による情報は、あなたの保険の詳細を提供します。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross를 통한 커버리지와 관련 정보를 포함하고 있을 수 있습니다. 귀하신 귀하의 건강 커버리지 계획 유지를 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 것입니다. 귀하에 이러한 정보를 얻으시려면 귀하의 연락처 번호가 필요할 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하시오.

 простой (Farsi):
این اطلاعات ممکن است جایگزین اطلاعات مهم بمانند. این اطلاعات به زبان های مختلف می‌باشند. این اطلاعات جایگزین اطلاعات مهم بمانند. این اطلاعات به زبان های مختلف می‌باشند. این اطلاعات جایگزین اطلاعات مهم بمانند. این اطلاعات به زبان های مختلف می‌باشند. این اطلاعات جایگزین اطلاعات مهم بمانند. این اطلاعات به زبان های مختلف می‌باشند. این اطلاعات جایگزین اطلاعات مهم بمانند. این اطلاعات به زبان های مختلف می‌باشند. این اطلاعات جایگزین اطلاعات مهم بمانند. این اطلاعات به زبان های مختلف می‌باشند. این اطلاعات جایگزین اطلاعات مهم بمانند. این اطلاعات به زبان های مختلف می‌باشند. این اطلاعات جایگزین اطلاعات مهم بمانند. این اطلاعات به زبان های مختلف می‌باشند. این اطلاعات جایگزین اطلاعات مهم بمانند. این اطلاعات به زبان های مختلف می‌باشند. این اطلاу

پنجابی (Punjabi):
نیکی پنجابی (Punjabi):

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Líame al 800-722-1471 (TTY: 800-842-5357).

Тагалог (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaring may mga mahalagang paksito dito sa paunawa. Maaring mangailangahan ka na magsagawa ng habang ka ilang mga tinakdang panahon unang mapanatili ang iyong aplikasyon sa kalusugan o tulong na may mga costos. May karapatan ka na makakaya ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

Thế Việt (Vietnamese):