**Name of Policy:**
Genetic Testing, Including Chromosomal Microarray (CMA) Analysis and Next Generation Sequencing Panels, for the Genetic Evaluation of Patients with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder

Policy #: 416  
Latest Review Date: March 2014
Category: Laboratory  
Policy Grade: A

**Background/Definitions:**
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Chromosomal microarray (CMA) testing has been proposed for detection of genetic imbalances in infants or children with characteristics of developmental delay/intellectual disability (DD/ID) or autism spectrum disorder (ASD). G-banded karyotyping has for many years been the standard first-line test for this purpose. G-banded karyotyping allows visualization and analysis of chromosomes for chromosomal rearrangements including genomic gains and losses. Chromosomal microarray (CMA) analysis performs a similar, although non-visual, analysis at a much higher resolution. As a result, CMA has the potential to increase the diagnostic yield in this population and change clinical interpretation in some cases.

Next-generation sequencing (NGS) panel testing allows for simultaneous analysis of a large number of genes and has been proposed as a way to identify single gene causes of syndromes that have autism as a significant clinical feature, in patients with normal CMA testing.

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 public health. Cases of developmental delay/intellectual disability (DD/ID) and of autism are 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 is used as a basis for establishing a diagnosis.

Current guidelines for these patients, such as those published by the American Academy of Pediatrics (AAP) and the American Academy of Neurology (AAN), recommend cytogenetic evaluation to look for certain kinds of chromosomal abnormalities that may be causally related to their condition. The AAN guidelines note that only in occasional cases will an etiologic diagnosis lead to specific therapy that improves outcomes, but suggest the more immediate clinical benefits of achieving a specific genetic diagnosis from the clinical viewpoint are as follows:

- Limit additional diagnostic testing;
- Anticipate and manage associated medical and behavioral comorbidities;
- Improve understanding of treatment and prognosis; and
- Allow counseling regarding risk of recurrence in future offspring and help with reproductive planning.

AAP and AAN guidelines also emphasize the importance of early diagnosis and intervention in an attempt to ameliorate or improve behavioral and cognitive outcomes over time.

Most commonly, genetic abnormalities associated with neurodevelopmental disorders are deletions and duplications of large segments of genomic material, which are called “copy number variants,” or CNVs. For many well-described syndromes, the type and location of the chromosomal abnormality has been established with the study of a large number of cases and...
constitutes 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 (e.g., G-banded) and fluorescence in situ hybridization (FISH), have relatively low resolution and a low diagnostic yield (i.e., proportion of tested patients found to have clinically relevant genomic abnormalities), leaving the majority of cases without identification of a chromosomal abnormality associated with the child’s condition. CMA 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.

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.

**Policy:**
Effective for dates of service on or after March 1, 2014:

I. **Testing in Children**

Chromosomal microarray analysis (CMA) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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 when all of the following conditions are met (see Policy Guidelines for definitions):

- Any indicated biochemical tests for metabolic disease have been performed, and results are non-diagnostic, **and**
- FMR1 gene analysis (for Fragile X), when clinically indicated, is negative, **and**
- In addition to a diagnosis of nonsyndromic DD/ID or ASD, the child has one or more of the following:
  - two or more major malformations, **or**
  - a single major malformation or multiple minor malformations, in an infant or child who is also small-for-dates, **or**
    - a single major malformation and multiple minor malformations, **and**
- The results for the genetic testing have the potential to impact the clinical management of the patient, **and**
- 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.

Chromosomal microarray analysis (CMA) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in all other cases of suspected genetic abnormality in
children with developmental delay/intellectual disability or autism spectrum disorder and is considered investigational.

**Chromosomal microarray analysis (CMA)** to confirm the diagnosis of a disorder or syndrome that is routinely diagnosed based on clinical evaluation alone (see Policy Guidelines) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Panel testing using next-generation sequencing does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder.

**II. Prenatal Testing**

**Chromosomal microarray analysis (CMA)** for prenatal genetic testing meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the following condition:

- Evaluating fetuses with structural abnormalities detected on fetal ultrasound or fetal magnetic resonance imaging.

**Chromosomal microarray analysis (CMA)** for prenatal gene mutations in fetuses without structural abnormalities (e.g., advanced maternal age, positive maternal serum screen, previous trisomy) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Panel testing using next-generation sequencing for prenatal genetic testing does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in all cases.

**Chromosomal microarray analysis (CMA)** for prenatal genetic testing does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

**Policy Guidelines:**

Definitions, from the American College of Medical Genetics Guideline, Evaluation of the Newborn with Single or Multiple Congenital Anomalies:

- A malformation refers to abnormal structural development.
- A major malformation is a structural defect that has a significant effect on function or social acceptability. Examples: ventricular septal defect or a cleft lip.
- 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.
- 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.

In some cases of CMA analysis, the laboratory performing the test confirms all reported CNVs with an alternative technology such as fluorescence in situ hybridization (FISH) analysis.

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Effective for dates of service from January 27, 2013 through February 28, 2014:

Policy:

Chromosomal microarray analysis (CMA) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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 when all of the following conditions are met (see Policy Guidelines for definitions):

- Any indicated biochemical tests for metabolic disease have been performed, and results are non-diagnostic, and
- FMR1 gene analysis (for Fragile X), when clinically indicated, is negative, and
- In addition to a diagnosis of nonsyndromic DD/ID or ASD, the child has one or more of the following:
  - two or more major malformations, or
  - a single major malformation or multiple minor malformations, in an infant or child who is also small-for-dates, or
    - a single major malformation and multiple minor malformations, and
- The results for the genetic testing have the potential to impact the clinical management of the patient, and
- 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.

Chromosomal microarray analysis (CMA) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in all other cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder and is considered investigational.

Chromosomal microarray analysis (CMA) to confirm the diagnosis of a disorder or syndrome that is routinely diagnosed based on clinical evaluation alone (see Policy Guidelines) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Chromosomal microarray analysis (CMA) for prenatal genetic testing does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.
Policy Guidelines:
Definitions, from the American College of Medical Genetics Guideline, Evaluation of the Newborn with Single or Multiple Congenital Anomalies:

- A malformation refers to abnormal structural development.
- A major malformation is a structural defect that has a significant effect on function or social acceptability. Examples: ventricular septal defect or a cleft lip.
- 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.
- 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.

In some cases of CMA analysis, the laboratory performing the test confirms all reported CNVs with an alternative technology such as fluorescence in situ hybridization (FISH) analysis.

Effective for dates of service prior to January 26, 2013:
Chromosomal microarray analysis (CMA) (targeted or whole-genome) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in the evaluation of children with cognitive developmental delay/intellectual delay or autism spectrum disorder and is considered investigational.

Chromosomal microarray analysis (CMA) for prenatal genetic testing does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
This policy is based on a TEC Special Report on array comparative genomic hybridization (aCGH). Since that Report was written, the technology has rapidly increased in resolution, and chromosomal microarray (CMA) has become the term of general use to accommodate all variations in the technology. Increased resolution arrays have been quickly translated to clinical services with a resulting increase in diagnostic yield, but also an increase in the potential for results of undetermined significance. Surveys conducted two to three years ago indicated that
there is a lack of consensus between laboratories in the interpretation and reporting of copy number variants (CNVs), particularly those that are challenging. The International Standards for Cytogenomic Arrays (ISCA) database now offers increased standardization and classification of CNVs that have been previously reported and should improve consensus in reporting.

**CMA analysis to determine genetic etiology**

CMA analysis detects copy number variants or CNVs by comparing a reference genomic sequence (“normal”) with the corresponding patient sequence. Each sample has a different fluorescent label so that they can be distinguished, and both are co-hybridized to a sample of a specific reference (also normal) DNA fragment of known genomic locus. 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 (e.g., a duplication of the same sequence), the sequence imbalance is detected as a difference in fluorescence intensity. For this reason, standard CMA (non-single nucleotide polymorphisms (SNP), see following) 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.

CMA analysis uses thousands of cloned or synthesized DNA fragments of known genomic locus immobilized on a glass slide (microarray) to conduct thousands of comparative reactions at the same time. The prepared sample and control DNA are hybridized to the fragments on the slide, and CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. Array resolution is limited only by the average size of the fragment used and by the chromosomal distance between loci represented by the reference DNA fragments on the slide.

There are some differences in CMA technology, most notably in the various types of microarrays. They can differ first by construction; earliest versions were used of DNA fragments cloned from bacterial artificial chromosomes (BAC). These have been largely replaced by oligonucleotide (oligos; short, synthesized DNA) arrays, which offer better reproducibility. Finally, arrays that detect hundreds of thousands of single nucleotide polymorphisms (SNP) across the genome have some advantages as well. Oligo/SNP hybrid arrays have been constructed to merge the advantages of each. Regardless of the array components used, all microarrays allow the deposition of many thousands of short, DNA probe sequences on a small, solid surface in an orderly fashion. The location of each known probe sequence allows the identification of the test sequence bound to it, and when compared to a control sequence, the identification of missing sequences or sequences with extra copies (i.e. copy number variants).

Microarrays may be prepared by the laboratory utilizing 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.
Targeted CMA analysis 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 but also recommends 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 accurately delineate breakpoints.

Whole-genome CMA analysis 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, MLPA, PCR).
- 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.
- A pathogenic etiology is additionally supported when a CNV includes a gene known to cause the phenotype when inactivated (microdeletion) or overexpressed (microduplication).
- 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 kb to 1 Mb.
- 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.

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. 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 online at: www.iscaconsortium.org/index.php); to date, it has established a public database containing de-identified whole genome microarray data from a subset of the ISCA Consortium member clinical diagnostic laboratories. Array analysis was carried out on
individuals with phenotypes including intellectual disability, autism, and developmental delay. As of November 2011, there are over 28,500 total cases in the database. 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 NCBI/NIH and curated by a committee of clinical genetics laboratory experts. A 2012 update from the ISCA summarizes their experience as a model for ongoing efforts to incorporate phenotypic data with genotypic data to improve the quality of research and clinical care in genetics.

Use of the database includes an intra-laboratory curation process, whereby laboratories are alerted to any inconsistencies amongst their own reported CNVs or other mutations, as well as any not consistent with the ISCA “known” pathogenic and “known” benign lists. The intra-laboratory conflict rate was initially about 3% overall; following release of the first ISCA curated track, the intra-laboratory conflict rate decreased to about 1.5%. A planned inter-laboratory curation process, whereby a group of experts curates reported CNVs/mutations across laboratories, is currently in progress.

The Consortium 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 defines levels of evidence (from the literature and/or the ISCA and other public databases) that describe how well or how poorly detected mutations or CNVs are correlated with phenotype. The consortium will apparently coordinate a volunteer effort to describe the evidence for targeted regions across the genome.

The consortium is also developing vendor-neutral recommendations for standards for the design, resolution, and content of cytogenomic arrays using an evidence-based process and an international panel of experts in clinical genetics, clinical laboratory genetics, genomics, and bioinformatics.

**Diagnosis of developmental delay/intellectual disability or autism spectrum disorder**

The diagnosis of developmental delay (DD) is reserved for children less than five years of age who have significant delay in two or more of the following developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living. The diagnosis implies developmental delays that may be significant and may predict life-long disability, although not all children diagnosed with DD will later be diagnosed with intellectual disability.

Intellectual disability (ID) is a life-long disability diagnosed at or after age five when intelligence quotient (IQ) testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV), defines patients with ID as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than two of areas of adaptive behavior or systems of support.

According to the DSM-IV, pervasive developmental disorders (PDD) encompass five conditions: autistic disorder, Asperger disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), childhood disintegrative disorder, and Rett syndrome. While the term autism spectrum disorder (ASD) is not mentioned in the DSM-IV, it is now accepted to include the first
In this list. However, ASD, PDD, and autism are often used interchangeably. These conditions are characterized by varying degrees of restrictions in communication and social interaction, and atypical behaviors.

Some children present with features of both DD/ID and of autism. For example, Yeargin-Allsopp et al reported that nearly 70% of children with a validated diagnosis of ASD, sampled from five metropolitan Atlanta counties, had cognitive impairment. The evaluation pathway depends on the pediatrician, consulting specialists, and their consensus on the primary neurodevelopmental diagnosis.

**Review of evidence**

**CMA**

**Post-natal CMA analysis**

Several studies have conducted CMA analysis on samples with known chromosom al abnormalities by standard karyotyping. In general, currently available CMA clinical services achieve 100% sensitivity for known chromosomal abnormalities. False-positive rates (i.e., CNVs of undetermined clinical significance) on known normal samples were inconsistently reported and could not be summarized. One study evaluated the analytic validity of an oligo array and reported 99% sensitivity and 99% specificity, with a resolution of 300–500 kilobases (Kb) for 10 selected cases with different known chromosomal abnormalities.

Several studies reported the diagnostic yield of CMA analysis in DD/ID or ASD patients with normal standard karyotype and in several cases normal FMR1 gene analysis and/or subtelomere FISH screening. Overall, diagnostic yield ranged from 5 to 16.7% in DD/ID patients and from 3.4 to 11.6% in patients with ASD; for this compilation, studies differed considerably in array resolution and in patient selection criteria. This compares well with a synthesis of studies recently published by the ISCA Consortium, reporting an average diagnostic yield of 12.2% across 33 studies. Hochstenback et al reported a CMA diagnostic yield of 19% for 36,325 DD/ID cytogenetic referrals in the Netherlands; and Shen et al. reported a 7% diagnostic yield among 933 ASD referrals. Cooper et al studied CMA analyses from over 15,000 individuals with DD/ID, ASD, and/or various congenital abnormalities and compared them to CMA analyses from over 8,000 unaffected controls, finding a significant excess of large CNVs among cases compared to controls. Using a common cutoff for CNV size, about 26% of cases had a CNV larger than 400 kilobases (kb) compared to about 12% of controls, suggesting that CNVs of this size account for approximately 14% of cases. CNVs larger than 400 kb were also significantly more common among cases with multiple congenital abnormalities.

Since the introduction of CMA analysis in about 2005, 18 new genomic disorders have been described, more than doubling the number of disorders described in the previous 20 years. Using CMA in place of conventional cytogenetic testing would have missed 0.6-0.8% of all cases, i.e., those with balanced translocations.

A portion of the increased diagnostic yield from CMA analysis 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. This contradicts earlier assumptions about inherited, apparently balanced rearrangements and shows that microarray analysis can allow for a less subjective and more accurate interpretation of an abnormal banding pattern.

Neither standard cytogenetic analysis nor CMA analysis have been systematically studied for impact on clinical outcomes other than diagnosis; Schaefer and Mendelsohn acknowledge, for example, that a genetic diagnosis “typically will not change interventions for the [autism] patient.” Rather, clinical utility of genetic testing is primarily inferred based on the value of diagnosis to the family, estimation of recurrence risk, and on the importance of early detection and early intervention. Two studies indirectly addressed clinical outcomes other than diagnosis as a result of CMA analysis.

Saam et al interviewed 14 physicians (2 neurologists, 12 medical geneticists) regarding management changes as a result of positive CMA test results from the University of Utah Cytogenetics Laboratory for 48 patients with developmental delay or intellectual disability and normal karyotypes. Only 29 percent of patients had no management changes reported. For significant proportions of patients, the diagnostic odyssey was ended. However, this study was only a survey and did not attempt to quantitate the diagnostic tests avoided. Saam et al also reported that 14.6% of patients with genetic diagnoses were referred to medical specialists and 25% had improved access to insurance and educational services, but the study did not assess the benefits of specialist referrals or screening for comorbidities on patient outcomes, or describe and quantitate the improvement in access to community services.

Coulter et al identified and reviewed, over the course of one year, the medical records of all patients at a tertiary children’s hospital who had CMA results showing an abnormal variant or a variant of possible significance. A board-certified medical geneticist reviewed the clinical notes from the ordering provider and abstracted recommendations for clinical actions (a specialist referral, imaging study, diagnostic test, or medication prescription) made specifically as a result of the CMA result. Of 1,792 patients for whom CMA was ordered during the year reviewed, 131 had an abnormal variant and 104 had a variant of possible significance. Of these, 121 and 73 patients were included in the analysis. Overall, patients with an abnormal variant had a significantly higher rate of recommended clinical action (54%) than patients with a variant of possible significance (34%; p=0.01). Among patients with an abnormal variant and a diagnosis of DD/ID or congenital anomalies, about two-thirds of patients were referred for additional clinical action based on the CMA results, whereas referrals were made for 27% of patients with ASD and an abnormal variant. Referral rates were similar for patients with a CMA result of a variant of possible significance, with the exception of patients with congenital anomalies, who were referred for additional clinical action only 17% of the time. Patients younger than two years were significantly more likely to have clinical anomalies and were significantly more likely to have abnormal variants. Cases were described in which ancillary CMA results suggested clinical interventions for the present or future regarding possible co-morbid conditions. In no patients, however, were referrals linked to actual patient outcomes; the authors report that this study is ongoing.
Risk estimates for recurrence of disease in future births can be altered considerably by information from the genetic diagnosis. For example, the average sibling recurrence risk in ASD is 5%. However, if the cause is a dominant single gene disorder with full penetrance and a parent is a carrier, the sibling risk is 50%. If the disorder is recessive but characteristics are otherwise the same, the sibling risk is 25%. If the cause is Fragile X, the recurrence risk in a brother is 50%, while a sister may be only mildly affected but will have a carrier risk of up to 50%. However, in the case of a de novo CNV (i.e., not carried by either parent), the sibling risk remains low, at the population average.

Knowledge of recurrence risk is expected to lead to improved future reproductive decision-making in families with children affected with DD/ID or ASD associated with specific mutations. Turner et al studied the reproductive decisions of women from 38 families characterized by male members with intellectual disability and a pattern consistent with chromosome X-linked transmission. Most of the women in these families spent many years knowing that they were at some risk of being carriers and of having a boy with ID. Prior to the availability of pathogenic mutation analysis, the birth rate for these families was below average for the district (United Kingdom-New South Wales), 1 in 27 versus 1 in 11 per year, respectively. After pathogenic mutation status was determined, both carriers and non-carriers (previously thought to be at risk) of the mutation had children at same rate with 74% of carriers choosing prenatal genetic evaluation. While the results of this study are suggestive, they do not show that knowledge of recurrence risk directly affected reproductive decisions. Saam et al, in the survey described previously, reported that recurrence risk evaluation was possible in about one-third of families after positive CMA results, but did not study the impact of recurrence risk evaluation on reproductive planning.

As noted in the Description, guidelines emphasize the importance of cytogenetic evaluation to look for certain kinds of mutations that may be linked to specific conditions for early diagnosis and intervention. However, the benefits of early intervention for these disorders are uncertain. Few randomized trials have been conducted, and the interventions differ considerably in the available studies, indicating that the field is still early in researching the critical elements of effective early intervention. For well-characterized genetic syndromes, it may be important to incorporate monitoring for comorbidities known to be associated with the condition. For example, 22q11 microdeletion syndrome (includes diGeorge and velo-cardio-facial syndromes) is associated with development of hearing impairment in a significant proportion of patients and subsequent delayed speech. Velo-cardio-facial syndrome is also associated with heart defects. Klinefelter syndrome may first be detected as developmental delay in early childhood; androgen treatment is an important component of therapy. CMA analysis may also predict future conditions for which interventions are possible. In a report of three cases, one patient had a chromosomal deletion that included a gene associated with autosomal dominant Peutz-Jeghers syndrome (PJS); tumor screening protocols for males with PJS generally begin with upper and lower endoscopy with small-bowel follow-through radiographs beginning at age eight years. Two other patients had a de novo deletion of chromosome 17p encompassing the TP53 tumor suppressor gene responsible for Li-Fraumeni syndrome (LFS); tumor screening protocols for LFS also begin in childhood. In another report, a child presenting to a neurology service with unusual behaviors was found to have a deletion that included exons of the DMD gene associated with Becker muscular dystrophy (BMD). Additional testing revealed a markedly elevated
creatine kinase, and a thorough physical exam was consistent with BMD. This diagnosis explained some of the child’s behavior and prompted a plan for future surveillance for cardiac and other complications of BMD, as well as carrier testing and surveillance of the child’s mother.

Ellison and colleagues reported on the clinical utility of CMA in a total of 46,298 postnatal patients. Testing was for a variety of indications, including developmental delay/intellectual disability (DD/ID), congenital anomalies, dysmorphic features and neurobehavioral problems. The authors tallied the detection of abnormalities associated with actionable clinical features (i.e., diagnoses which would likely lead to changes in clinical management). A total of 2,088 diagnoses were made of 118 clinically actionable disorders; of these, it was estimated that 94% would likely have been missed by routine karyotyping. Examples of clinically actionable responses to the diagnoses included an electrocardiogram and cardiology referral for those at risk for long QT syndrome, glucose monitoring and endocrine referral for those at increased risk of diabetes, renal ultrasound for those at risk for renal pathology and platelet count monitoring for those at risk for thrombocytopenia. A subset of cases was monitored for physician response to the microarray finding, and appropriate clinical action was taken more than 90% of the time.

Prenatal CMA analysis
Prenatal fetal karyotyping is a routine test initiated when the fetus is believed to be at high risk for a chromosomal abnormality as a result of a structural abnormality identified during an ultrasound exam, because of family history, or for other reasons agreed on by the patient and physician. However, karyotyping provides useful information in only a small percentage of these cases. Consistent with the increased diagnostic yield of CMA analysis, many laboratories are now providing this service in the prenatal setting. Currently, the microarrays used in this setting are most often targeted arrays used to reduce the number of results of uncertain significance and thus reduce parent anxiety and difficulties in decision making. However, whole-genome analysis is also available.

Hillman et al conducted a systematic review and meta-analysis of studies reporting CMA analysis results in the prenatal setting or in the immediate postnatal setting after pregnancy termination for structural abnormalities detected by ultrasound. A total of 751 participants in eight studies were included for the overall meta-analysis; 409 of these had fetal anomalies using ultrasound. Overall, CMA analysis detected 3.6% more chromosomal imbalances than karyotyping when CMA results of unknown significance were included (1.1%). The CMA excess detection rate was higher in those with fetal anomalies by ultrasound, at 5.2% including results of unknown significance (1.9%). CMA analysis failed to detect one case of triploidy, and, as would be expected of the standard CMA technology, also failed to detect 14 cases of balanced translocations. The authors note the benefit of the additional detection by CMA but also the increase in results of unknown significance, and discuss the difficulties of interpretation in conjunction with prenatal decision making.

Wapner et al conducted a prospective study to evaluate the accuracy, efficacy and incremental yield of CMA, as compared with karyotyping for routine prenatal diagnosis. A total of 4,406 women undergoing routine prenatal diagnosis in one of 29 diagnostic centers by either chorionic villus sampling (CVS) or amniocentesis had a sample split in two for standard karyotyping and
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Medical Policy #416

CMA. Indications for prenatal diagnosis included advanced maternal age (AMA) (46.6%), a positive aneuploidy screening result (18.8%), structural anomalies detected by ultrasound (U/S) (25.2%) and other indications (9.4%). CMA analysis was successful in 98.8% of the fetal samples. The primary analysis classified microarray results as being true positive, true negative, false positive or false negative relative to the findings by karyotyping. Secondary outcomes included the occurrence and classification of CNVs identified by microarray in the presence of a normal karyotype and the ability of CMA to identify uncommon cytogenetic abnormalities found on karyotyping. Two array platforms were used, one covering targeted regions of known disease association, and one genome-wide SNP assay. The data for the second platform were masked by the analysis software to emulate the same resolution and coverage as the first platform; therefore, review of the SNPs was not performed. Microarray analysis of DNA from maternal and paternal blood samples was used to determine whether CNVs detected in fetal samples were inherited. All de novo array findings seen in samples with a normal karyotype were confirmed by a second method, preferentially FISH. Deletions and duplications identified exclusively by means of microarray analysis were classified as “pathogenic” when they encompassed a region implicated in a well-described abnormal phenotype, and all other deletions and duplications were classified as being of “uncertain clinical significance”. A total of 4,282 samples were included in the primary analysis. Of these, common autosomal aneuploidies were identified in 7.4% and sex-chromosome aneuploidies were identified in 1.3% by standard karyotyping. CMA identified all of these aneuploidies. None of the balanced rearrangements identified on karyotyping were identified with CMA, nor did CMA identify any of the triploid samples (0.4%). Of the 3,822 cases with a normal karyotype, on microarray, 1,399 samples were identified as having CNV; of these, 88.2% were classified as common benign. 0.9% were on the predetermined list of pathogenic CNVs. The cases of uncertain clinical significance were adjudicated by a Clinical Advisory Committee, which reclassified them as likely to be benign (1.8% of all 1,399 samples), and of potential clinical significance (1.6% of all 1,399 samples). Overall, a total of 96 of the 3,822 fetal samples with normal karyotypes (2.5%; 95% confidence interval [CI]: 2.1-3.1) had a microdeletion or duplication of clinical significance.

In subgroup analysis of women with normal karyotypes, samples from fetuses with suspected growth or structural anomalies, 6.0% (95% CI: 4.5-7.9) had clinically relevant findings on microarray. Of the women tested for advanced maternal age, 1.7% (95% CI: 1.2-2.4) had a clinically relevant finding on microarray, as did 1.6% (95% CI: 0.9-2.9) of women who tested positive on Down’s syndrome screening. Recurrent CNVs associated with autism and neurocognitive alterations were detected in 1.3% of karyotypically normal pregnancies: 3.6% with and 0.8% without structural anomalies.

In summary, in this study, microarray analysis provided additional clinically relevant information in 1.7% of pregnancies with standard indications for prenatal diagnosis (eg, advanced maternal age, positive aneuploidy screening test) and in 6.0% of cases with an anomaly on ultrasound.

Breman et al evaluated the prenatal CMA results on greater than 1,000 fetal samples sent for testing at Baylor College of Medicine Medical Genetics Laboratories between 2005 and 2011. A total of 1,124 specimens were received, of which reportable results were obtained in 1,115. Maternal blood samples were required with every fetal sample, (and paternal if possible), to
exclude maternal cell contamination and to assist with interpretation of CNVs. The chromosomal microarray analysis (CMA) was performed on DNA extracted from amniotic fluid, chorionic villus sampling (CVS) or cultured cells (amniocytes/CVS) in most of the cases. The gestational ages for direct amniotic fluid samples ranged from 14 to 36 weeks; samples from pregnancies that were more than 16 weeks’ gestation provided the most optimal DNA yield. Samples were submitted for either standard cytogenetic studies (karyotype with or without aneuploidy FISH) plus CMA, or for CMA only with a karyotype analysis having been performed elsewhere. For those samples, unless only DNA was submitted, a culture was established in the Baylor laboratory so that any CMA findings could be confirmed by an independent method (FISH, karyotype, or other). The most common clinical indications were abnormal ultrasound findings (n=410) and advanced maternal age (n=394). Other indications included a previous child with or a family history of a genetic disorder or chromosome abnormality (n=137), further workup of a known chromosomal abnormality detected by karyotype or FISH (n=61), parental concern (n=61), an abnormal maternal serum screen (n=37) and other or unclassified (n=4). Twelve cases had no indication provided. The cases spanned five years, over which time, different types of targeted clinical arrays were used, with progressively increasing complexity and sensitivity. Targeted BACs were used for 282 samples, and all others with targeted oligonucleotide arrays. In 881 (79%) of the 1,115 samples, no deletions or duplications were observed using prenatal CMA analysis. Copy number changes were detected in 234 (21%) cases. Of these, 131 (11.7%) were classified as likely benign. Eighty-five cases (7.6%) were found to have clinically significant genomic imbalances. Twenty seven microdeletion or microduplication findings (2.4% of total cases; or 32% of abnormal cases) were small gains or losses below the resolution of prenatal karyotype analysis, and would not have been detected by conventional chromosome studies alone. Of these, family history was the indication for testing in eight cases, an abnormal FISH result was the indication for one case, and the remaining 18 abnormal findings were unanticipated. Eighteen specimens out of the total 1,115 (1.6%) had results of uncertain clinical significance. An additional 17 cases were found to have multiple inherited CNVs interpreted as likely benign familial variants. The indications yielding the greatest number of clinically significant findings by microarray analysis were abnormal karyotype/FISH (42.6%), a family history of chromosomal abnormality (9.5%), all abnormal prenatal ultrasound findings (9.3%), abnormal serum screening (5.4%) and advanced maternal age (1.3%). In summary, the overall detection rate for clinically significant CNVs was 7.6%; the detection rate was 4.2% when the abnormal cases that had a previously identified chromosome abnormality or a known familial genomic imbalance were excluded. In 1.7% of the cases, abnormal results were obtained that were neither anticipated prior to microarray analysis nor detectable by conventional prenatal chromosome analysis. The clinical significance of the microarray results could not be determined in 1.7% of cases.

In summary, in prenatal specimens, targeted or lower resolution arrays have the ability to detect the majority of clinically relevant alterations while maintaining a low rate of results with unclear significance. However, this is associated with an increased risk of missing a pathogenic abnormality in a region not covered sufficiently by a targeted array. In addition, many of the known genomic disorders that can be detected on targeted arrays are not associated with readily detectable fetal abnormalities on prenatal ultrasound examinations. Higher resolution arrays have a greater chance of detecting a larger number of alterations but also will have more results of unknown clinical significance.
NGS
Analytic validity (the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent)

No peer-reviewed, full-length publications on the analytic validity of the commercially available NGS ASD panels are identified.

Clinical validity (the diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease)

No peer-reviewed, full-length publications on the clinical validity of the commercially available NGS ASD panels are identified.

According to one laboratory’s website, this type of sequencing will pick up more than 97% of DNA mutations at the level of a few base pairs, but that for most genes on the panel, the clinical sensitivity of the assay cannot be estimated individually, because each gene is a rare cause of ASD.

Clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes)

No peer-reviewed, full-length publications on the clinical utility of the commercially available NGS ASD panels are identified.

Importantly, no published data on the rate of variants of unknown significance using NGS panels for autism have been identified.

Clinical Input Received through 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. In response to requests, clinical input was received through three physician specialty societies and two academic medical centers while this policy was under review in early 2010. Those providing input supported use of targeted CMA analysis in children with DD/ID or ASD 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.

In 2011, clinical input was obtained with emphasis on the clinical utility of CMA testing. As in 2010, reviewers supported the use of CMA testing for the diagnosis in patients with development disorders 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.

Summary
Postnatal CMA analysis
CMA analysis offers a higher resolution approach to detecting the presence of chromosomal alterations that have been associated with cases of developmental delay/intellectual disability or autism spectrum disorder compared to karyotyping and ancillary testing. However, the diagnostic yield remains low in unselected populations without accompanying signs and/or symptoms. In individuals with apparent nonsyndromic developmental delay, intellectual disability, or suspected autism spectrum disorder and accompanying malformations, the diagnostic yield is much higher and is higher than the yield of karyotype testing.

Evidence on the clinical benefit of CMA testing is largely anecdotal. Cases have been documented in which the information derived from testing ends a long diagnostic odyssey, aids in planning for surveillance or management of associated comorbidities, and assists in future reproductive decision making. While systematic studies of the impact of CMA analysis on patient outcomes is lacking, the improvement in diagnostic yield has been well-demonstrated, and feedback from physician specialty societies, academic medical centers, and in respected guidelines is consistent in supporting the clinical benefit of CMA testing for defined populations. As a result, chromosomal microarray analysis may be considered medically necessary in individuals with developmental delay or autism spectrum disorders who meet the clinical criteria defined the policy statement.

Prenatal CMA analysis
When used in prenatal cases where there is an abnormality detected on ultrasound and a normal karyotype, CMA testing will detect clinically relevant abnormalities in a small percentage of cases. For routine screening of pregnant women, the yield of abnormal findings is less and the clinical utility of CMA in detecting chromosomal abnormalities in prenatal specimens is unknown. The potential risk for findings of uncertain clinical significance may result in parental anxiety and challenges in genetic counseling. As a result, the use of CMA analysis in the prenatal setting may be considered medically necessary in patients who meet the clinical criteria defined in the policy statement.

NGS panels
Published data on analytic and clinical validity, clinical utility and variants of unknown significance using next-generation sequencing (NGS) panels in this setting are lacking, and therefore, panel testing using NGS is considered investigational in all cases of suspected genetic abnormality in children with DD/ID or ASD and in all cases of prenatal testing.

Practice Guidelines and Position Statements
American Congress of Obstetricians and Gynecologists Committee Opinion 581, 2013:
The College and the Society for Maternal-Fetal Medicine offer the following recommendations for the use of CMA in prenatal diagnosis:
• In patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis,
chromosomal microarray analysis is recommended. This test replaces the need for fetal karyotype.

- In patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.
- Most genetic mutations identified by chromosomal microarray analysis are not associated with increasing maternal age; therefore, the use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older.
- In cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired, chromosomal microarray analysis on fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended because of its increased likelihood of obtaining results and improved detection of causative abnormalities.
- Limited data are available on the clinical utility of chromosomal microarray analysis to evaluate first-trimester and second-trimester pregnancy losses; therefore, this is not recommended at this time.

(There is controversy as to the sensitivity of routine ultrasound in detecting fetal anomalies. A review of 36 studies involving more than 900,000 fetuses found an overall sensitivity of 40.4% [range, 13.3%- 82.4%]. Studies on the use of ultrasound to detect prenatal anomalies vary with regard to the definition of major versus minor fetal anomalies, the level of risk in the study population [high vs low risk], the expertise of the ultrasound operators and the ascertainment of anomalies).

The American Academy of Neurology and the Practice Committee of the Child Neurology Society updated their guideline regarding the evaluation of unexplained global developmental delay/intellectual disability with information on genetic and metabolic (biochemical) testing in order 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 acknowledge that “Research is sorely lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis.”

The American College of Medical Genetics (ACMG) published guidelines on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. Chromosomal microarray testing for copy number variation is 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 developmental delay/ intellectual disability
C. Autism spectrum disorders

ACMG also recommends against use of CMA in cases of multiple miscarriages.

Additional ACMG guidelines have been published for 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 (see Description). A 2013 update includes

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recommendations for validation of microarray methodologies for both prenatal and postnatal specimens.

The International Standard Cytogenomic Array Consortium published a Consensus Statement in which they recommend 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 FISH test such as subtelomeric FISH, and the yield is greater.”

A 2013 guidelines update from the ACMG states that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of autism spectrum disorder is recommended, with the recommendation being for first-tier to include FXS [fragile X syndrome] and CMA, and second tier to include MECP2 and PTEN testing. The guideline states 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.”

Key Words:
Array Comparative Genomic Hybridization, aCGH, developmental delay, DD, mental retardation, MR, autism, pervasive developmental disorders, PDD, Asperger disorder, autism spectrum disorder, ASD, Array CGH, Chromosomal Microarray Analysis, CMA, intellectual disability, SignatureChip® OS, Signature PrenatalChip® TE, GenomeDx, postnatal microarray, prenatal microarray, Prenatal Targeted Array

Approved by Governing Bodies:
CMA analysis and NGS are commercially available from several laboratories as a laboratory-developed test. Laboratory-developed tests performed by laboratories licensed for high complexity testing under the Clinical Laboratory Improvement Amendments (CLIA) do not require U.S. Food and Drug Administration (FDA) clearance for marketing.

At a meeting hosted by the FDA in July 2010, the FDA indicated that the Agency will in the future require microarray manufacturers to seek clearance in order to sell their products for use in clinical cytogenetics. Criteria for clearance, however, have not yet been published.

On January 17, 2014, FDA cleared for marketing the Affymetrix CytoScan® Dx Assay. FDA reviewed the Affymetrix CytoScan Dx Assay through its de novo classification process. For the de novo petition, 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 when compared with several analytically validated test methods. FDA found that the CytoScan Dx Assay could analyze a patient’s entire genome and adequately detect chromosome variations in regions of the genome associated with intellectual and developmental disabilities.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
CPT Codes:
- **81228** Cytogenomic 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) (Effective 01/01/2012)
- **81229** Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities (Effective 01/01/2012)
- **81479** Unlisted molecular pathology procedure

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

**Previous Coding:**
CPT Codes:
There is no specific CPT coding for this testing. It may be reported using a combination of molecular diagnostic codes (83890-83914) and array-based evaluation of molecular probes codes (88384-88386). (Deleted 01/01/2013)

**References:**


**Policy History:**
Medical Policy Group, February (1)
Medical Policy Administration Committee, February 2010
Available for comment February 23-April 8, 2010
Medical Policy Group, December 2011 (1): Added new 2012 CPT codes
Medical Policy Group, January 2012 (1): Update to Title, Description, Policy, Key Points, Key Words and References related to MPP update. Change from array comparative genomic hybridization to chromosomal microarray analysis and mental retardation to intellectual disability throughout policy. No change in policy coverage criteria.
Medical Policy Group, November 2012 (1): Update to Policy with Policy Guidelines, Description, Key Points, Governing Bodies and References related to coverage criteria for CMA for diagnosing genetic abnormalities in DD/ID or autism spectrum disorder
Available for comment December 12, 2012 through January 26, 2013
Medical Policy Panel, January 2013
Medical Policy Group, February 2013 (1) Update to Key Points, Key Words and References; no change to policy statement
Medical Policy Panel, March 2013
Medical Policy Group, March 2014 (1): Update to Key Points, Key Words, Coding and References related to addition of coverage criteria for prenatal testing and noncoverage of NGS
Medical Policy Administration Committee, April 2014
Available for comment April 4 through May 19, 2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.