

Corporate Medical Policy

Chromosomal Microarray (CMA) Analysis for Genetic Evaluation of Developmental Delay/Autism Spectrum Disorder

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Description of Procedure or Service

G-banded karyotyping has for many years been the standard first-line test for detection of genetic imbalances in infants or children with characteristics of developmental delay/mental retardation or autism spectrum disorder. G-banded karyotyping allows visualization and analysis of chromosomes for chromosomal rearrangements including genomic gains and losses. Chromosomal microarray (CMA) analysis performs a similar function, but at a much higher resolution. As a result, CMA increases the diagnostic yield in this population and can change clinical interpretation in some cases.

Children with signs of neurodevelopmental delays or disorders in the first few years of life may eventually be diagnosed with developmental delay or autism syndromes, serious and lifelong conditions that present significant challenges to families and to public health. Cases of developmental delay 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 genetic testing of specific genes associated with the diagnosed syndrome. However, for children who do not present with an obvious syndrome, who are too young for full expression of a suspected syndrome, or who may have an atypical presentation, genetic testing may be used as a basis for establishing a diagnosis.

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 guidelines suggest the more immediate clinical benefits of achieving a specific genetic diagnosis from the clinical viewpoint are as follows:

- end the diagnostic odyssey and allay parents' fears about other causes;
- guide optimal management and surveillance e.g., of associated comorbidities;
- refer patients to an appropriate specialist;
- determine possible prognosis; and
- advise on risk of recurrence in future offspring or in extended family.

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.

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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 with clinically relevant genomic abnormalities), leaving the majority of cases without identification of a chromosomal abnormality associated with the child's condition. CMA analysis 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.

Chromosomal Microarray (CMA) to determine genetic etiology

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 genomic hybridization (CGH) reactions at the same time. CGH detects CNVs by comparing a normal genomic sequence ("control") with the corresponding patient sequence. Patient and control samples are each labeled with a different fluorochrome so that they can be distinguished. Sequence imbalance is detected as a difference in bound fluorescence intensity between patient and control samples. The CGH reaction 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 differ between patient and control.

There are various types of microarrays. They can differ first by construction; earliest versions were composed of cloned DNA fragments from bacterial artificial chromosomes (BAC). These have been largely replaced by oligonucleotide (short, synthesized DNA) arrays, which offer better reproducibility. Finally, arrays that detect hundreds of thousands of single nucleotide polymorphisms (SNP) across the genome have the advantage of being able to detect uniparental disomy in addition to the detectable by the oligo arrays. Oligo/SNP hybrid arrays have been constructed to merge the advantages of each.

Targeted CMA analysis provides high-resolution coverage of the genome primarily in areas containing known, clinically significant CNVs. Targeted arrays have been largely relegated to prenatal testing because whole-genome arrays, which provide high resolution coverage of the entire genome, also allow discovery of new CNVs.

Of the major laboratories offering this type of testing, most appear to use whole genome oligo arrays with anywhere from 44 to 180k oligos per array, and average genome backbone probe spacing ranging from 22 to 35kb, with higher density in regions of known clinical significance. However, some labs use whole genome SNP or oligo/SNP hybrid arrays.

Such discoveries have resulted in the characterization of several new genetic syndromes by CMA analysis, 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 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

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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). (3)
- 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 500 kb to 2 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.

In 2008, the International Standards for Cytogenomic Arrays (ISCA) Consortium was organized (<https://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 March 2011, there are 24,271 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. Using the ISCA database, along with other genomic and genetics databases, the Consortium will develop recommendations for the interpretation and reporting of pathogenic versus benign copy number changes, as well as imbalances of unknown clinical significance.

The Consortium also plans to develop 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.

Regulatory Status

CMA analysis is 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.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for chromosomal microarray analysis when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

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When Chromosomal Microarray Analysis for Genetic Evaluation of Patients with Developmental Delay or Autism Spectrum Disorder is covered

Chromosomal microarray analysis (targeted or whole-genome) is considered **medically necessary** in the evaluation of children with the following conditions who otherwise would undergo testing using G-banded karyotyping and subtelomeric FISH:

- Multiple anomalies not specific to a well-delineated genetic syndrome, or
- Apparently non-syndromic developmental delay/ intellectual disability, or Autism spectrum disorders.

When Chromosomal Microarray Analysis for Genetic Evaluation of Patients with Developmental Delay or Autism Spectrum Disorder is not covered

Chromosomal microarray analysis is considered investigational for prenatal genetic testing.

Policy Guidelines

Chromosomal microarray analysis is considered first-line testing in the clinical situations noted above, i.e., this testing is performed before (instead of) karyotyping.

Except in very unusual cases, both CMA and karyotyping are not needed in the diagnostic evaluation.

Although a different laboratory technology, CMA analysis provides results that are, with few minor exceptions, equivalent to those of G-banded karyotyping and FISH subtelomere analysis, clinically-accepted tests for the DD/MR and ASD childhood populations. In addition, CMA analysis provides greatly increased resolution such that diagnostic yield is improved by approximately a factor of 2. With increased resolution, more results of uncertain significance are being reported. A recently established public database to which major clinical laboratories are contributing data will inform CMA analysis and minimize uncertainty of results. Additional efforts toward microarray standardization should also assist with consensus in the field.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81229

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: aCGH for the Genetic Evaluation of Patients with Developmental Delay/Mental Retardation or

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Autism Spectrum Disorder. TEC Assessments 2009; 24 (Tab 10)

Stankiewicz P, Beaudet AL. Use of array CGH in the evaluation of dysmorphology, malformations, developmental delay, and idiopathic mental retardation. *Curr Opin Genet Dev* 2007; 17(3):182-92.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.59, 2/11/2010

Senior Medical Director Review 3/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.59, 4/14/2011

Policy Implementation/Update Information

- 4/12/11 New policy developed. Array CGH (targeted or whole-genome) is considered investigational in the evaluation of children with cognitive developmental delay or autism spectrum disorder. Array CGH is considered investigational for prenatal genetic testing. (adn)
- 8/16/11 Policy name changed from: Array Comparative Genomic Hybridization for Genetic Evaluation to Chromosomal Microarray Analysis for Genetic Evaluation. The term "array comparative genomic hybridization (aCGH)" was changed to "chromosomal microarray (CMA) analysis" throughout policy. Policy statement changed to indicate testing may be medically necessary in the evaluation of children with the following conditions who otherwise would undergo testing using G-banded karyotyping and subtelomeric FISH: Multiple anomalies not specific to a well-delineated genetic syndrome, or apparently non-syndromic developmental delay/ intellectual disability, or autism spectrum disorders. Description section, Policy Guidelines section and Reference section updated. Specialty Matched Consultant Advisory panel review 7/27/11. Policy accepted as drafted. (adn)
- 1/24/12 Added CPT code 81229 to "Billing/Coding" section. (sk)

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