Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder

Description of Procedure or Service

Chromosomal microarray analysis (CMA) can identify genomic abnormalities that are associated with a wide range of developmental disabilities, including cognitive impairment, behavioral abnormalities, and congenital abnormalities. CMA testing can detect copy number variants (CNVs) and the frequency of disease-causing CNVs is highest (20%-25%) in children with moderate-to-severe intellectual disability accompanied by malformations or dysmorphic features. Disease-causing CNVs have been identified in 5% to 10% of cases of autism, being more frequent in severe phenotypes.

Developmental Delay/Intellectual Disability and Autism Spectrum Disorder

Children with signs of neurodevelopmental delays or disorders in the first few years of life may eventually be diagnosed with intellectual disability or autism syndromes, serious and lifelong conditions that present significant challenges to families and to public health. Developmental delay/intellectual disability (DD/ID) and of autism spectrum disorder (ASD) may be associated with genetic abnormalities. For children with clear, clinical symptoms and/or physiologic evidence of syndromic neurodevelopmental disorders, diagnoses are based primarily on clinical history and physical examination, and then may be confirmed with 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.

The diagnosis of DD is reserved for children younger than 5 years of age who have significant delay in 2 or more of the following developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living.

ID is a life-long disability diagnosed at or after 5 years of age when intelligence quotient (IQ) testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), of the American Psychiatric Association defines patients with ID as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than 2 areas of adaptive behavior or systems of support.

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

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

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

Congenital Anomalies

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

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

- limit further diagnostic testing
- anticipate and manage associated medical and behavioral comorbidities;
- improve understanding of treatment and prognosis; and
- allow for counseling regarding risk of recurrence, and prevent recurrence through screening for carriers and prenatal testing.

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

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

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

Conventional methods of cytogenetic analysis, including karyotyping (eg, G-banded) and FISH, have relatively low resolution and a low diagnostic yield (ie, proportion of tested patients found to have clinically relevant genomic abnormalities), leaving most cases without identification of a chromosomal abnormality associated with the child’s condition. CMA 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.

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.

CMA to determine genetic etiology

The term CMA collectively describes 2 different array platforms: aCGH and SNP arrays. Both types of arrays can identify loss or gain of DNA (microdeletions or microduplications, respectively), known as CNVs.

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

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

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

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

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

Microarrays may be prepared by the laboratory 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 (eg, FISH, multiplex ligation-dependent probe amplification, polymerase chain reaction).
- CNVs detected are checked against public databases and, if available, against private databases maintained by the laboratory. Known pathogenic CNVs associated with the same or similar phenotype as the patient are assumed to explain the etiology of the case; known benign CNVs are assumed to be nonpathogenic.
- 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 cut-off; 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, to promote consistency among laboratories and CMA results. Three categories of clinical significance are recommended for reporting: pathogenic, benign, and uncertain clinical significance.
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In 2008, the International Standards for Cytogenomic Arrays (ISCA) Consortium was organized; it has established a public database containing deidentified whole genome microarray data from a subset of the ISCA Consortium member clinical diagnostic laboratories. Array analysis was carried out on individuals with phenotypes including DD/ID and ASD. As of August 2016, there are over 53,000 subjects with individual-level 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. In 2011, Kaminsky and colleagues used data from the ISCA consortium, including 15,749 cases and 10,118 published controls available at the time of analysis, to identify the functional significance of 14 rare CNVs in intellectual and developmental disabilities, and to describe a methodology for assessing for pathologic CNVs. In this study, the frequency of pathogenic CNVs was 17.1%

Next-Generation Sequencing

Next-generation sequencing (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 SNPs, CNVs, and insertions and deletions. With higher resolution comes higher likelihood of detection of variants of uncertain clinical significance.

Commercially available tests

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

Affymetrix CytoScan Dx has been cleared by the U.S. Food and Drug Administration (FDA) through the de novo 510(k) process. FDA’s review of the CytoScan Dx Assay included an analytic evaluation of the test’s ability to accurately detect numerous chromosomal variations of different types, sizes, and genome locations compared with several analytically validated test methods. FDA found that the CytoScan Dx Assay could analyze a patient’s entire genome and adequately detect chromosome variations in regions of the genome associated with ID/DD. Reproducibility decreased with the CNV gain or loss size, particularly when less than approximately 400 kilobases (kb; generally recommended as the lower reporting limit).

FirstStepDx PLUS (Lineagen, Salt Lake City, UT) uses Lineagen’s custom-designed microarray platform manufactured by Affymetrix. This microarray consists of 1,953,246 unique nonpolymorphic probes and 743,304 SNP probes that come standard on the Affymetrix CytoScan HD® microarray, with an additional 83,443 custom probes designed by Lineagen.

Ambry Genetics (Aliso Viejo, CA) offers multiple tests (CMA and NGS) that are designed for ASD and neurodevelopmental disorders.

LabCorp offers the Reveal SNP Microarray-Pediatric for individuals with nonsyndromic congenital anomalies, dysmorphic features, DD/ID, mental retardation, and/or ASD.

Next Generation Sequencing (NGS)
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.

Courtagen (Woburn, MA) offers 3 NGS panels which are intended for the assessment of developmental and behavioral phenotypes:
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- devSEEK® Triome™: includes 1119 genes associated with DD/ID and ASD.
- devSEEK®: includes 237 genes associated with DD/ID and ASD, with additional testing available for large deletions and duplications.
- devACT® Clinical Management Panel: includes 250 genes associated with DD/ID and ASD, focusing on genes associated with actionable clinical management changes, with additional testing available for large deletions and duplications.

Emory Genetics Laboratory offers a NGS ASD panel of genes that target genetic syndromes that include autism or autistic features.

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

Regulatory Status

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

In July 2010, FDA indicated that it will in the future require microarray manufacturers to seek clearance to sell their products for use in clinical cytogenetics.

On January 17, 2014, FDA cleared for marketing the Affymetrix CytoScan® Dx Assay. FDA reviewed the Affymetrix CytoScan® Dx Assay through the 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.

Related Policies: Genetic Testing for FMR1 Mutations Including Fragile X Syndrome

***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 genetic testing for evaluation of developmental delay/autism spectrum disorder 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.

When Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder is covered
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Chromosomal microarray analysis is considered **medically necessary** as first-line testing in the initial postnatal evaluation of individuals with any of the following:

- Apparently nonsyndromic developmental delay/intellectual disability
- Autism spectrum disorder
- Multiple congenital anomalies not specific to a well-delineated genetic syndrome

**When Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder is not covered**

Panel testing using next-generation sequencing is considered investigational in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder.

**Policy Guidelines**

**Chromosomal Microarray Analysis**

The evidence for CMA testing in individuals who have DD/ID, ASD, or multiple congenital anomalies not specific to a well-delineated genetic syndrome primarily includes case series. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. Evidence supports test accuracy and validity. Although systematic studies of the impact of CMA on patient outcomes are lacking, the improvement in diagnostic yield over karyotyping has been well demonstrated. While direct evidence of improved outcomes with CMA compared with karyotype is lacking, for at least a subset of the disorders potentially diagnosed with CMA in this patient population, there are well-defined and accepted management steps associated with positive test results. Further, there is evidence of changes in reproductive decision making as a result of positive test results.

The information derived from CMA testing can: end a long diagnostic odyssey, result in a reduction in morbidity for certain conditions with initiation of surveillance or management of associated comorbidities, and may impact future reproductive decision making for parents and potentially the affected child. Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

**Next-Generation Sequencing Panels**

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

**Practice Guidelines and Position Statements**

The American Academy of Neurology and the Child Neurology Society updated their guidelines on the evaluation of unexplained global DD/ID with information on genetic and metabolic (biochemical) testing to accommodate advances in the field. The guidelines conclude that CMA testing has the highest diagnostic yield in children with DD/ID, that the often complex results require confirmation and careful interpretation, “often with the assistance of a medical geneticist,” and that CMA should be considered the “first-line” test. The guidelines acknowledge that “Research is sorely lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis.”
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The American College of Medical Genetics (ACMG) published guidelines on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. CMA testing for copy number variation (CNV) 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 nonsyndromic developmental delay/intellectual disability  
C. ASD

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. A 2013 update includes recommendations for validation of microarray methodologies for both prenatal and postnatal specimens.

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

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

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: 81228, 81229, 81470, 81471, S3870

At this time, there are no specific CPT codes for next-generation sequencing panels. They would be reported with the unlisted molecular pathology code 81479.

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


Senior Medical Director Review 3/2011


Specialty Matched Consultant Advisory Panel 7/2012


Specialty Matched Consultant Advisory Panel review 1/2013


Specialty Matched Consultant Advisory Panel review 1/2014

Medical Director review 1/2014

Policy re-titled Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder

Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder


Senior Medical Director review 10/2014

Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Medical Director review 3/2016


Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder


Medical Director review 8/2016


Specialty Matched Consultant Advisory Panel review 3/2017

Medical Director review 3/2017

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)

8/7/12 Description section updated. When Covered and When Not Covered sections updated. The following investigational statement was added: “Chromosomal microarray analysis is considered investigational in all other cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder.” The following not medically necessary statement was added: “Chromosomal microassay analysis to confirm the diagnosis of a disorder or syndrome that is routinely diagnosed based on clinical evaluation alone is not medically necessary.” Policy guidelines updated. Specialty Matched Consultant Advisory Panel Review 7/18/12. Notification given 8/7/12 for policy effective date of 11/13/12. (sk)

2/12/13 Specialty Matched Consultant Advisory Panel review 1/2013. References updated. Description section updated with new commercially available tests. Policy Guidelines updated to include information on prenatal CMA analysis. No changes to Policy Statements. (mco)

12/31/13 S3870 added to Billing/Coding section. (mco)


Policy re-titled Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder
Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder

4/29/14  Policy retitled from “Chromosomal Microarray Analysis for Genetic Evaluation of Developmental Delay/Autism Spectrum Disorder” to “Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder.” Information regarding Next Generation Sequencing (NGS) testing added throughout policy. Description section updated. Policy statement revised to state: “BCBSNC will provide coverage for genetic testing for evaluation of developmental delay/autism spectrum disorder when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.” The following statement added to the “When not Covered” section: “Panel testing using next-generation sequencing is considered investigational in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder.” Added the following statement to the Billing/Coding section: “At this time, there are no specific CPT codes for next-generation sequencing panels. They would be reported with the unlisted molecular pathology code 81479.” Policy Guidelines updated. References updated. Medical Director review 4/2014.

11/11/14  References updated. Description section updated. “When Covered” section updated to remove this statement, “Chromosomal microarray analysis is considered investigational for prenatal genetic testing”. Policy Statements unchanged. Senior Medical Director review 10/2014. (td)

12/30/14  Added CPT codes 81470 and 81471 to the Billing/Coding section effective as of 1/1/2015. (td)


10/1/15  Description section extensively revised. When Covered statement changed to include Chromosomal Microarray analysis may be considered medically necessary for apparently nonsyndromic developmental delay/intellectual disability, autism spectrum disorder, and multiple anomalies not specific to a well-delineated genetic syndrome. When Not Covered section updated to state, “Panel testing using next-generation sequencing is considered investigational in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder”. Policy Guidelines section extensively revised. References updated. (td)


9/30/16  Description section updated, adding NGS description information. Policy Guidelines and references updated. Medical Director review 8/2016. (jd)


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