Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder

Description of Procedure or Service

Developmental Delay/Intellectual Disability and Autism Spectrum Disorder

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

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

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

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

Autism Spectrum Disorder

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

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

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

A large body of evidence supports a genetic etiology in ASD. Twin studies estimate heritability between 60% and 90%. A family with an affected child has a 13% to 19% risk for recurrence in subsequent children. Based on Swedish genetic studies, Gaugler and colleagues (2014) concluded that “the bulk of autism arises from genetic variation” (as opposed to environmental causes). Still, although genetic determinants can be heritable, most appear to arise de novo.

For these reasons, a child with ASD is often evaluated with genetic testing. Testing may be targeted when a child has a recognizable syndrome for example, FMR1 (fragile X), MECP2 (Rett), and PTEN.

**Diagnostic Testing**

**Karyotyping and FISH**

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

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

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

**Chromosomal Microarrays**

Two types of CMAs are considered here: array comparative genomic hybridization (aCGH) and single nucleotide variants (SNVs) arrays. The aCGH approach uses DNA samples from a patient and a normal control. Each is labeled with distinct fluorescent dyes (red or green). The labeled samples are then mixed and hybridized to thousands of cloned or synthesized reference (normal) DNA fragments of known genomic locus, immobilized on a glass slide (microarray), to conduct thousands of comparative reactions simultaneously. CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. If the patient sequence is missing part of the normal sequence (a deletion) or has the normal sequence plus
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additional genomic material within that genomic location (eg, a duplication), the sequence imbalance is detected as a difference in fluorescence intensity. For this reason, aCGH cannot detect balanced chromosomal translations (equal exchange of material between chromosomes) or sequence inversions (same sequence is present in reverse base pair order) because the fluorescence intensity would not change. A portion of the increased diagnostic yield from CMA over karyotyping comes from the discovery that chromosomal rearrangements that appear balanced (and therefore not pathogenic) by G-banded karyotype analysis are found to have small imbalances with greater resolution. It has been estimated that 40% of apparently balanced de novo or inherited translocations with abnormal phenotype are associated with cryptic deletion if analyzed by CMA testing.

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

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

Next-Generation Sequencing

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

Genetic Associations With DD/ID and ASD

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

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

**Commercially available tests**

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

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

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

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

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

**Next Generation Sequencing (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. Emory Genetics Laboratory offers an NGS ASD panel of genes targeting genetic syndromes that include autism or autistic features.

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

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

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

Chromosomal microarray analysis is considered medically necessary as first-line testing in the initial 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

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

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 validity, changes in reproductive decision making, morbid events, and resource utilization.

Evidence supports test validity. Although systematic studies of the impact of CMA on patient outcomes are lacking, the improvement in diagnostic yield over karyotyping has been well demonstrated. 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 testing in this patient population, there are well-defined and accepted
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management steps associated with positive test results. Further, there is evidence of changes in reproductive decision making as a result of positive test results. The information derived from CMA testing can accomplish the following: end a long diagnostic odyssey, reduce morbidity for certain conditions by initiating surveillance or management of associated comorbidities; or it may impact future reproductive decision making for parents and potentially the affected child. Therefore, the evidence is sufficient to determine 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 validity, changes in reproductive decision making, morbid events, and resource utilization. The diagnostic yield 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.”

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 variations (CNVs) 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.”

Billing/Coding/Physician Documentation Information
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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

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
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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


Senior Medical Director review 10/2014

Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Medical Director review 3/2016
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Medical Director review 8/2016


Specialty Matched Consultant Advisory Panel review 3/2017

Medical Director review 3/2017


Medical Director review 8/2017

Specialty Matched Consultant Advisory Panel review 3/2018

Medical Director review 3/2018


Medical Director review 10/2018

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-delimited 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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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 microarray 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

4/29/14  Policy re-titled 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...
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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)


9/15/17 Description section extensively revised for better flow of policy and updates under “Commercially available tests” updated. Removed “postnatal” from the When Covered section and added: “Chromosomal microarray is considered investigational for the evaluation of all other conditions of delayed development, including but not limited to idiopathic growth or language delay” to When Not Covered section. No change to policy intent. References updated. Medical Director review. (jd)


11/9/18 Description section extensively revised, minor revision to policy guidelines. References updated. Medical Director review 10/2018. (jd)

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