Medical Policy

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

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Policy Number: 228
BCBSA Reference Number: 2.04.59
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
- Invasive Prenatal (Fetal) Diagnostic Testing, #708
- Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss, #686

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Testing in children
Chromosomal microarray analysis may be 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.

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

Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

This is not a covered service.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
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<tr>
<td>Commercial Managed Care (HMO and POS)</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
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<td>This is not a covered service.</td>
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<tr>
<td>Medicare PPO Blue℠</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tr>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
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<tr>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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HCPCS Codes

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<th>HCPCS codes:</th>
<th>Code Description</th>
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<tr>
<td>S3870</td>
<td>Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation</td>
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The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

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<th>CPT codes:</th>
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<td>81470</td>
<td>X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2</td>
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<tr>
<td>81471</td>
<td>X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2</td>
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Description

Chromosomal microarray (CMA) analysis can identify genomic abnormalities 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.1,2

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.

The diagnosis of developmental delay (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. Intellectual disability (ID) is a life-long disability diagnosed at or after 5 years of age when IQ testing is considered valid and reliable.

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), of the American Psychiatric Association defined 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, autism spectrum disorder (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.

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.

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.3 Genetic factors have been identified as 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 (eg, DiGeorge/velocardiofacial syndrome, cri-du-chat syndrome, 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 a neonate with congenital anomalies, because a patient’s clinical presentation may be atypical or have nonspecific phenotypic features that may be shared by several different disorders, or a young patient 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).

Genetic Associations with DD/ID, ASD, and Congenital Anomalies
DD/ID and 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 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 may be used as a basis for establishing a diagnosis.

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 autism cases, 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 not 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.

Guidelines for patients with ID/DD, ASD, and/or congenital anomalies, such as those published by the American Academy of Pediatrics5 (AAP) and the American Academy of Neurology6 (AAN) with the Child Neurology Society (CNS), have recommended cytogenetic evaluation to look for certain kinds of chromosomal abnormalities that may be causally related to their condition. The joint AAN and CNS guidelines have noted that only occasionally 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 follows6:

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

The AAP and the AAN and CNS joint guidelines have also emphasized 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.7 This is not yet a major clinical use of testing and is not a focus in this review.

Testing to Determine Genetic Etiology
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 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 testing 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 Testing**

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.

**Array Comparative Genomic Hybridization and Single-Nucleotide Polymorphism**

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, 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 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 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.9

**Copy Number Variants**

Targeted CMA 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.9-11
- A pathogenic etiology is additionally supported when a CNV includes a gene known to cause the phenotype when inactivated (microdeletion) or overexpressed (microduplication).10
- 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.11-14
- 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.9,15

ACMG has also published guidelines for the interpretation and reporting of CNVs in the postnatal setting, to promote consistency among laboratories and CMA results.16 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; 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 subjects with phenotypes including DD/ID and ASD. As of August 2016, there were over 53,000 subjects with individual-level data 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 National Center for Biotechnology Information/NIH and curated by a committee of clinical genetics laboratory experts. In 2011, Kaminsky et al 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**

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**

**CMA Analysis**

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, and/or ASD.

**Next-Generation Sequencing**

A variety of commercial and academic laboratories offer NGS panels designed for the evaluation of ASD, DD/ID, and congenital anomalies, which vary in terms of the numbers of and specific genes tested. Courtagen (Woburn, MA) offers 3 NGS panels intended for the assessment of developmental and behavioral phenotypes:

- **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 an NGS ASD panel of genes targeting genetic syndromes that include autism or autistic features.

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

**Summary**

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), autism spectrum disorder (ASD), and/or congenital anomalies. CMA testing increases the diagnostic yield over karyotyping in this population and may impact clinical management decisions. 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.

For individuals who have DD/ID, ASD, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive CMA testing, the evidence includes primarily case series. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. The available 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 karyotyping 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. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have DD/ID, ASD, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive NGS panel testing, the evidence includes primarily 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.

**Policy History**

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<td>10/2016</td>
<td>BCBSA National medical policy review.</td>
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<td>1/2016</td>
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<td>New medically necessary indications described. Clarified coding information. Effective 1/1/2016</td>
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<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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<td>Prenatal testing removed from this policy and added to new policy #708, Invasive Prenatal (Fetal) Diagnostic Testing. Policy #708 is effective 3/1/2015.</td>
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<td>Clarified coding information.</td>
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<td>8/2014</td>
<td>BCBSA national medical policy review. New investigational indications described. Title changed to include NGS. Effective 8/1/2014.</td>
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<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<td>Removed ICD-9 diagnosis codes 315.00, 315.01, 315.02, 315.1, 315.2, 315.31, 315.32, 315.34, 315.35, 315.39, 315.4, 315.5, and 315.8 as they do not meet the intent of the policy. Added ICD-9 diagnosis codes 299.00, 299.01, 299.10, 299.11 299.80, 299.81, 299.90, 299.91.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


