Genetic Testing, Including Chromosomal Microarray Analysis and Next-Generation Sequencing Panels, for the Evaluation of Developmental Delay/Intellectual Disability, Autism Spectrum Disorder and/or Congenital Anomalies
Corporate Medical Policy

File name: Genetic Testing, Including Chromosomal Microarray Analysis and Next Generation Sequencing Panels, for the Evaluation of Developmental Delay/Intellectual Disability, Autism Spectrum Disorder and/or Congenital Anomalies
File code: UM.GEN.01
Origination: 7/2011
Last Review: 08/2015
Next Review: 08/2016
Effective Date: 1/1/2016

Description

Chromosomal microarray analysis (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 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.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With developmental delay/intellectual disability</td>
<td>• Chromosomal microarray analysis testing</td>
<td>• No chromosomal microarray analysis testing</td>
<td>• Test accuracy</td>
</tr>
<tr>
<td>• With autism spectrum disorder</td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
<tr>
<td>• With multiple congenital anomalies not specific to a well-delineated genetic syndrome</td>
<td></td>
<td></td>
<td>• Changes in reproductive decision making</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resource utilization</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With developmental delay/intellectual disability</td>
<td>• Next-generation sequencing panel testing</td>
<td>• No next-generation sequencing panel testing</td>
<td>• Test accuracy</td>
</tr>
<tr>
<td>• With autism spectrum disorder</td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
<tr>
<td>• With multiple congenital anomalies not specific to a well-delineated genetic syndrome</td>
<td></td>
<td></td>
<td>• Changes in reproductive decision making</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resource utilization</td>
</tr>
</tbody>
</table>
Policy

Coding Information

Click the links below for attachments, coding tables & instructions.
Attachment I- CPT & HCPCS Code List & Instructions
Attachment II- ICD-10 List

When a service may be considered medically necessary

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

When a service is considered investigational

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

Policy Guidelines

A 2013 guidelines update from American College of Medical Genetics (ACMG) states that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of autism spectrum disorder is recommended, with the recommendation being for first tier to include fragile X syndrome and chromosomal microarray analysis (CMA).

In some cases of CMA, the laboratory performing the test confirms all reported copy number variants with an alternative technology such as fluorescent in situ hybridization analysis.

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.

Background

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 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. Cases of developmental delay/intellectual disability (DD/ID) and 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 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.

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.

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%)-

---

Page 3 of 23
Medical Policy Number: UM.GEN.01
(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, they may 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 additional diagnostic testing;
- anticipate and manage associated medical and behavioral comorbidities;
- improve understanding of treatment and prognosis; and
- allow counseling regarding risk of recurrence in future offspring and help with reproductive planning.

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

Most commonly, genetic abnormalities associated with neurodevelopmental disorders are deletions and duplications of large segments of genomic material, 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 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:

- aCGH 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. Consanguinity is of concern in that offspring of closely related parents carry an increased risk of an autosomal recessive disease compared with the general population. 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.

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.

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 has allowed the characterization of several new genetic syndromes, with other potential candidates currently under study. However, the whole-genome arrays also have the disadvantage of potentially high numbers of apparent false-positive results, because benign CNVs are also found in phenotypically normal populations; both benign and pathogenic CNVs are continuously cataloged and, to some extent, made available in public reference databases to aid in clinical interpretation. Additionally, some new CNVs are neither known to be benign nor causal; these CNVs may require detailed family history and family genetic testing to determine clinical significance and/or may require confirmation by subsequent accumulation of similar cases and so, for a time, may be considered a CNV of undetermined significance (some may eventually be confirmed true positives or causal, others false positives or benign).
To determine clinical relevance (consistent association with a disease) of CNV findings, the following actions are taken:

- CNVs are confirmed by another method (e.g., FISH, 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 cutoff; potentially pathogenic CNVs are likely to be larger than benign polymorphic CNVs; cutoffs for CNVs not previously reported typically range from 300 kb to 1 Mb.
- Parental studies are indicated when CNVs of appropriate size are detected and not found in available databases; CNVs inherited from a clinically normal parent are assumed to be benign polymorphisms whereas those appearing de novo are likely pathogenic; etiology may become more certain as other similar cases accrue.

ACMG has also published guidelines for the interpretation and reporting of CNVs in the postnatal setting, to promote consistency among laboratories and CMA results. Three categories of clinical significance are recommended for reporting: pathogenic, benign, and uncertain clinical significance.

In 2008, the International Standards for Cytogenomic Arrays (ISCA) Consortium was organized (available at https://www.iscaconsortium.org/index.php); 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 November 2011, there were over 28,500 total cases in the database. Additional members are planning to contribute data; participating members use an opt-out, rather than an opt-in approach that was approved by the National Institutes of Health (NIH) and participating center institutional review boards. The database is held at National Center for Biotechnology Information/NIH and curated by a committee of clinical genetics laboratory experts. A 2012 update from ISCA summarizes its experience as a model for ongoing efforts to incorporate phenotypic data with genotypic data to improve the quality of research and clinical care in genetics.

Use of the database includes an intralaboratory curation process, whereby laboratories are alerted to any inconsistencies among their own reported CNVs or other mutations, as well as any inconsistent with the ISCA “known” pathogenic and “known” benign lists. The intralaboratory conflict rate was initially about 3% overall; following release of the first ISCA curated track, the intralaboratory conflict rate decreased to about 1.5%. A planned interlaboratory curation process, whereby a group of experts curates reported CNVs/mutations across laboratories, is currently in progress.
The Consortium recently proposed “an evidence-based approach to guide the development of content on chromosomal microarrays and to support interpretation of clinically significant copy number variation.” The proposal defines levels of evidence (from the literature and/or the ISCA and other public databases) that describe how well or how poorly detected mutations or CNVs are correlated with phenotype.

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

Commercially Available Tests

Chromosomal Microarray 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 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.

FirstStepDx PLUS is an integrated service that combines proprietary genetic testing, reporting, and genetic counseling.

Ambry Genetics offers a 180 K oligo array and a combined SNP plus aCGH and states that the tests should be considered for all individuals with syndromic or nonsyndromic conditions that may be caused by genomic imbalance.

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
Emory Genetics Laboratory offers an NGS ASD panel of 61 genes targeting genetic syndromes that include autism or autistic features. These genes have been associated with nonsyndromic autism and genes associated with conditions involved in the differential diagnosis of Rett syndrome and/or Angelman syndrome. The panel is offered as tier 2 testing after tier 1 cytogenetics, molecular, and biochemical testing, which includes array testing, fragile X CGG repeat analysis, and biochemical testing for some metabolic conditions.
Greenwood Genetics Center offers an NGS panel that includes 62 genes and flanking introns. The panel includes autosomal and X-linked genes representing the most common single-gene etiologies associated with a syndrome that includes autism as a significant clinical feature. The test is offered as an option for patients with syndromal autism and normal cytogenetic/array-based testing, or as a second-tier test for patients with a phenotype that resembles Rett or Angelman syndrome.

Both the Emory and Greenwood Genetics panels use RainDance technology, and the Greenwood Lab panel was developed jointly with Emory.

The Department of Genetics and Genomic Sciences at Mount Sinai School of Medicine offers a 30-gene sequencing panel.

Rationale

This evidence review was created in 2010, and has been updated regularly with a search of the MEDLINE literature, with the most recent review through June 15, 2015 (see Appendix Table 1 for genetic testing categories).

Chromosomal Microarray Analysis

Several studies (see Appendix B16) have conducted chromosomal microarray analysis (CMA) on samples with known chromosomal abnormalities by standard karyotyping. In general, currently available CMA clinical services achieve near 100% sensitivity for known chromosomal abnormalities. False-positive rates (ie, copy number variants [CNVs] of undetermined clinical significance) on known normal samples were inconsistently reported and could not be summarized. One study evaluated the analytic validity of an oligonucleotide (oligo) array and reported 99% sensitivity and 99% specificity, with a resolution of 300 to 500 kilobases (kb) for 10 selected cases with different known chromosomal abnormalities.

Several studies have reported the diagnostic yield of CMA in developmental delay/intellectual disability (DD/ID) or autism spectrum disorder (ASD) patients with normal standard karyotype and, in several cases, normal FMR1 gene analysis and/or subtelomere fluorescence in situ hybridization (FISH) screening (see Appendix C16). Overall, diagnostic yield ranged from 5% to 16.7% in DD/ID patients and from 3.4% to 11.6% in patients with ASD; for this compilation, studies differed considerably in array resolution and in patient selection criteria. This compares well with a synthesis of studies recently published by the International Standards for Cytogenomic Arrays (ISCA) Consortium, reporting an average diagnostic yield of 12.2% across 33 studies. Hochstenback et al reported a CMA diagnostic yield of 19% for 36,325 DD/ID cytogenetic referrals in the Netherlands; and Shen et al reported a 7% diagnostic yield among 933 ASD referrals. Cooper et al studied CMA from over 15,000 individuals with DD/ID, ASD, and/or various congenital abnormalities and compared them with CMA from over 8000 unaffected controls, finding a significant excess of large CNVs among cases compared with controls. Using a common cutoff for CNV size, about 26% of cases had a CNV larger than 400 kb compared with about 12% of controls, suggesting that CNVs of this size account for approximately 14% of cases. CNVs larger than 400 kb were also significantly more common among cases with multiple congenital abnormalities.
Hillman et al reported their experience with the use of the 105 K and 18 0K oligo microarrays in 215 consecutive patients who were referred with either autism or ASD or DD/learning disability for genetic services to a single medical center between 2009 and 2012. Of the 215 patients (140 males, 75 females), 65 had ASD and 150 had learning disability. Abnormal microarray results were found in 45 patients (21%) with a total of 49 CNVs. Thirty-two represented a known diagnostic CNV contributing to the clinical presentation and 17 represented variants of unknown significance. Thirteen of 65 patients (20%) with ASD had a CNV compared with 32 of 150 patients (21%) with a learning disability. The 13 patients with ASD had a total of 14 CNVs, 6 recognized as diagnostic and 8 as nondiagnostic. For those patients with a learning disability, 32 had a total of 35 CNVs, 26 of which were classified as a known diagnostic CNV (usually a deletion; n=20), and 9 were classified as an unknown nondiagnostic CNV (usually a duplication; n=8). A higher percentage of individuals with a learning disability had clinical findings of seizures, dysmorphic features, and microcephaly, but this was not statistically significant.

Lu et al reported on the frequency of genomic imbalances in neonates with birth defects by using 3 different targeted array comparative genomic hybridization (aCGH) platforms using bacterial artificial chromosomes. The study included 638 neonates with various birth defects who were referred between March 2006 and September 2007. Overall, 109 (17.1%) patients were identified with clinically significant CNVs, most of which would not have been defined by karyotyping. The clinically significant detection rates for various clinical indications were 66.7% for “possible chromosomal abnormality” ± “others” (other clinical indications), 33.3% for ambiguous genitalia ± others, 27.1% for dysmorphic features with multiple congenital anomalies ± others, 24.6% for dysmorphic features ± others, 21.8% for congenital heart disease ± others, 17.9% for multiple congenital anomalies ± others, and 9.5% for patients referred for other indications that were not in the defined groups. In all, of the 109 patients in whom clinically significant genomic imbalances or pathogenic CNVs were detected by CMA, 14.7% had numerical anomalies including trisomies 21, 18, 13, and 22, and monosomy X. The remaining 85.3% had genomic imbalances that may not have been detected by standard cytogenetic studies, including 33.9% with common microdeletion or microduplication syndromes, 40.4% with genomic imbalances at relatively rare disease loci, and 11.0% with chromosomal mosaicism.

**Clinical Utility of CMA Testing**

Neither standard cytogenetic nor CMA have been systematically studied for impact on clinical outcomes other than diagnosis; Schaefer and Mendelsohn24 acknowledged, eg, that a genetic diagnosis “typically will not change interventions for the [autism] patient.” Rather, clinical utility of genetic testing is primarily inferred based on the value of diagnosis to the family, estimation of recurrence risk, and on the importance of early detection and early intervention. Two studies indirectly addressed clinical outcomes other than diagnosis as a result of CMA.

Saam et al25 interviewed 14 physicians (2 neurologists, 12 medical geneticists) regarding management changes as a result of positive CMA test results from the University of Utah Cytogenetics Laboratory for 48 patients with DD or ID and normal karyotypes. Only 29% of patients had no management changes reported. For significant proportions of patients, the diagnostic odyssey was ended. However, this study was only a survey and did not quantify the diagnostic tests avoided. Saam et al also
reported that 14.6% of patients with genetic diagnoses were referred to medical specialists, and 25% had improved access to insurance and educational services, but the study did not assess the benefits of specialist referrals or screening for comorbidities on patient outcomes, or describe and quantify the improvement in access to community services.

Coulter et al identified and reviewed, over the course of 1 year, the medical records of all patients at a tertiary children's hospital who had CMA results showing an abnormal variant or a variant of possible significance. A board-certified medical geneticist reviewed the clinical notes from the ordering provider and abstracted recommendations for clinical actions (a specialist referral, imaging study, diagnostic test, or medication prescription) made specifically as a result of the CMA result. Of 1792 patients for whom CMA was ordered during the year reviewed, 131 had an abnormal variant and 104 had a variant of possible significance. Of these, 121 and 73 patients were included in the analysis. Overall, patients with an abnormal variant had a significantly higher rate of recommended clinical action (54%) than patients with a variant of possible significance (34%; p=0.01). Among patients with an abnormal variant and a diagnosis of DD/ID or congenital anomalies, about two-thirds of patients were referred for additional clinical action based on the CMA results, whereas referrals were made for 27% of patients with ASD and an abnormal variant. Referral rates were similar for patients with a CMA result of a variant of possible significance, with the exception of patients with congenital anomalies, who were referred for additional clinical action only 17% of the time. Patients younger than 2 years were significantly more likely to have clinical anomalies and were significantly more likely to have abnormal variants. Cases were described in which ancillary CMA results suggested clinical interventions for the present or future regarding possible comorbid conditions. In no patients, however, were referrals linked to actual patient outcomes; the authors reported that this study is ongoing.

Risk estimates for recurrence of disease in future births can be altered considerably by information from the genetic diagnosis. For example, the average sibling recurrence risk in ASD is 5%. However, if the cause is a dominant single-gene disorder with full penetrance and a parent is a carrier, the sibling risk is 50%. If the disorder is recessive but characteristics are otherwise the same, the sibling risk is 25%. If the cause is fragile X, the recurrence risk in a brother is 50%, while a sister may be only mildly affected but will have a carrier risk of up to 50%. However, in the case of a de novo CNV (ie, not carried by either parent), the sibling risk remains low, at the population average.

Knowledge of recurrence risk is expected to lead to improved future reproductive decision making in families with children affected with DD/ID or ASD associated with specific mutations. Turner et al 28 studied the reproductive decisions of women from 38 families characterized by male members with and a pattern consistent with chromosome X-linked transmission. Most women in these families spent many years knowing that they were at some risk of being carriers and of having a boy with mental retardation. Before the availability of pathogenic mutation analysis, the birth rate for these families was below average for their geographic area, 1 in 27 versus 1 in 11 per year, respectively. After pathogenic mutation status was determined, both carriers and noncarriers (previously thought to be at risk) of the mutation had children at the same rate, with 74% of carriers choosing prenatal genetic evaluation. While the
results of this study are suggestive, they do not show that knowledge of recurrence risk directly affected reproductive decisions. Saam et al, in the survey described previously, reported that recurrence risk evaluation was possible in about one-third of families after positive aCGH results but did not study the impact of recurrence risk evaluation on reproductive planning.

As noted in the Background section, guidelines emphasize the importance of cytogenetic evaluation to look for certain kinds of mutations that may be linked to specific conditions for early diagnosis and intervention. However, the benefits of early intervention for these disorders are uncertain. Few randomized trials have been conducted, and the interventions differ considerably in the available studies, indicating that the field is still early in researching the critical elements of effective early intervention. For well-characterized genetic syndromes, it may be important to incorporate monitoring for comorbidities known to be associated with the condition. For example, 22q11 microdeletion syndrome (includes DiGeorge and velocardiofacial syndromes) is associated with development of hearing impairment in a significant proportion of patients and subsequent delayed speech. Velocardiofacial syndrome is also associated with heart defects. Klinefelter syndrome may first be detected as DD in early childhood; androgen treatment is an important component of therapy. CMA may also predict future conditions for which interventions are possible. In a report of 3 cases, 1 patient had a chromosomal deletion that included a gene associated with autosomal-dominant Peutz-Jeghers syndrome (PJS); tumor screening protocols for males with PJS generally begin with upper and lower endoscopy with small-bowel follow-through radiographs beginning at age 8 years. Two other patients had a de novo deletion of chromosome 17p encompassing the TP53 tumor suppressor gene responsible for Li-Fraumeni syndrome; tumor screening protocols for Li-Fraumeni syndrome also begin in childhood. In another report, a child presenting to a neurology service with unusual behaviors was found to have a deletion that included exons of the DMD gene associated with Becker muscular dystrophy (BMD). Additional testing revealed a markedly elevated creatine kinase, and a thorough physical exam was consistent with BMD. This diagnosis explained some of the child’s behavior and prompted a plan for future surveillance for cardiac and other complications of BMD, as well as carrier testing and surveillance of the child’s mother. Ellison et al reported on the clinical utility of CMA in a total of 46,298 postnatal patients. Testing was for a variety of indications, including DD/ID, congenital anomalies, dysmorphic features, and neurobehavioral problems. The authors tallied the detection of abnormalities associated with actionable clinical features (ie, diagnoses that would likely lead to changes in clinical management). A total of 2088 diagnoses were made for 118 clinically actionable disorders; of these, it was estimated that 94% would likely have been missed by routine karyotyping. Examples of clinically actionable responses to the diagnoses included an electrocardiogram and cardiology referral for those at risk for long QT syndrome, glucose monitoring and endocrine referral for those at increased risk of diabetes, renal ultrasound for those at risk for renal pathology, and platelet count monitoring for those at risk for thrombocytopenia. A subset of cases was monitored for physician response to the microarray finding, and appropriate clinical action was taken more than 90% of the time.

This evidence review was originally based on a 2009 TEC Special Report on aCGH. A 2015 TEC Special Report on the use of CMA for the genetic evaluation of patients with DD/ID and ASD found the following for the clinical utility of CMA testing:
• Studies on the potential impact of CMA on clinical decisions “collectively indicate that identified pathogenic variants can prompt clinical actions potentially impacting morbidity. Less clear is how often outcomes will be improved and in which cases interventions might have occurred in the absence of testing. The proportion that may benefit will depend on the variants identified as well as diagnostic yield, which in turn depends on phenotype severity. Studies did not report on any follow-up or management changes in patients without identified pathogenic variants. In addition to reducing morbidity, bringing closure to a diagnostic odyssey is a reason for genetic testing ... and noted as an outcome in case series and reports. Parents cite obtaining services and support as a reason for testing, but the frequency and can impact on outcomes is difficult to quantify. The studies reviewed convey a set of intermediate outcomes likely to favorably affect the health of some children. Lacking are end-to-end cohort studies following children at presentation to final outcomes.” “There are considerable challenges conducting studies of sufficient size given the underlying genetic heterogeneity, and including follow-up adequate to observe final health outcomes”; however, “studies examining clinical utility have reported intermediate outcomes and indirect evidence.”

• “In addition, outside readily recognizable syndromes, pathogenic variants identified represent a collection of rare disorders. Ascertaining improved net health outcome for rare diseases is not easy. Both conditions and outcomes can be heterogeneous. The evidence reviewed here reflects the accompanying uncertainty, but supports a perspective that identifying a pathogenic variant can: (1) impact the search for a diagnosis, (2) inform follow-up that can benefit a child by reducing morbidity and rarely potential mortality, and (3) affect reproductive planning for parents and later potentially the affected child. There are also likely circumstances where other family members may be impacted owing to the nature of the variant and subsequent cascade (family member) testing. The downsides to testing can include detecting nonpaternity, an incorrect diagnosis, and findings of uncertain significance how often they occur is uncertain. It is difficult to quantify lower or upper bounds for any potential improvement in the net health outcome owing in part to heterogeneity of disorders, rarity, and outcome importance that may differ according to identified variants. The strong expert opinion in recommending initial CMA testing over other approaches ... together with the indirect evidence for benefit following testing, supports concluding that the net health outcome can be improved.

• “...[A] child with ASD appears to impact reproductive decision making, or so-called reproductive stoppage.” “Whether it can be attributed to concerns over having another affected child or the caregiving burden of the first affected child is unclear. Regardless, quantifying recurrence risk may assist reproductive decision making, particularly given that recurrence risk may be high—eg, in ASD, as high as 18%. However, establishing a genetic cause may revise the estimated risk considerably....”

• Wood et al analyzed reproductive stoppage and ASD recurrence rates within 2 U.K. family databases 299 families including 660 children (327 diagnosed with ASD). In 10% of families, there was more than 1 ASD-affected child and an estimated 24.7% recurrence risk. Reproductive stoppage was examined by
comparing statistically whether children with ASD were born later in families than their unaffected siblings. In 132 of the 180 complete families analyzed, the last-born child was more often affected (p<0.05); 40 families had a single child (affected) and 62 families 2 children with only the second affected. Any potential confounding by maternal or paternal age was not reported.

In June 2015, the Agency for Healthcare Research and Quality (AHRQ) issued a technical brief “Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder,” which summarized information on genetic tests (not limited to CMA) available in the United States for GDD/ID and ASD. The report also sought to identify studies supporting clinical utility, but did “not systematically review existing evidence addressing the tests’ clinical utility” or suggest an analytic framework for an indirect chain of evidence. The Technical Brief therefore lacked a synthesis of the body of evidence on clinical utility.

**Next-Generation Sequencing**

**Analytic Validity**

Analytic validity is the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent.

No peer-reviewed, full-length publications on the analytic validity of the commercially available next-generation sequencing (NGS) ASD panels were identified.

**Clinical Validity**

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

No peer-reviewed, full-length publications on the clinical validity of the commercially available NGS ASD panels were identified. According to 1 laboratory’s website, this type of sequencing will pick up more than 97% of DNA mutations at the level of a few base pairs, but, for most genes on the panel, the clinical sensitivity of the assay cannot be estimated individually, because each gene is a rare cause of ASD.

**Clinical Utility**

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

No peer-reviewed, full-length publications on the clinical utility of the commercially available NGS ASD panels were identified. Importantly, no published data on the rate of variants of unknown significance using NGS panels for autism have been identified.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in May 2015 did not identify any ongoing or unpublished trials that would likely influence this policy.
Summary of Evidence

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, and studies have documented that 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 is lacking. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011 Input
In 2011, clinical input was obtained with emphasis on the clinical utility of CMA testing. As in 2010, reviewers supported the use of CMA testing for the diagnosis in patients with DD and ASD. Reviewers acknowledged the lack of evidence in the literature on clinical utility, such as the lack of literature demonstrating improved outcomes as a result of testing. Reviewers cited multiple anecdotal and theoretical clinical situations in which management changes resulted from results of CMA testing. Reviewers also agreed that this test was widely used in standard care with the support of the genetics community.

2010 Input
In response to requests, clinical input was received through 3 physician specialty societies and 2 academic medical centers while this policy was under review in early 2010. Those providing input supported use of targeted CMA in children with DD/ID or ASD in several situations. There was less support for whole-genome array testing.
However, targeted array testing is now primarily available for prenatal analysis, whereas whole-genome arrays are recommended as standard.

Practice Guidelines and Position Statements

American Academy of Neurology
The American Academy of Neurology and the Practice Committee of 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.”

American College of Medical Genetics
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 update 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.”

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

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 Act (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 its de novo classification process. For the de novo petition, FDA’s review of the CytoScan Dx Assay included an analytic evaluation of the test’s ability to accurately detect numerous chromosomal variations of different types, sizes, and genome locations 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. FDA product code: PFX.

Reference Resources


**Document Precedence**

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract language, the member’s contract language takes precedence.

**Audit Information**

BCBSVT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.

**Administrative and Contractual Guidance**

**Benefit Determination Guidance**

Prior approval is required and benefits are subject to all terms, limitations and conditions of the subscriber contract.

An approved referral authorization for members of the New England Health Plan (NEHP) is required. A prior approval for Access Blue New England (ABNE) members is required. NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member’s health plan.

Federal Employee Program (FEP) members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure.

Coverage varies according to the member’s group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through a self-funded (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member’s plan documents or contact the customer service department.

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/2011</td>
<td>New policy</td>
</tr>
<tr>
<td>9/2012</td>
<td>Minor format changes made. Added file code name . Added “Document</td>
</tr>
</tbody>
</table>
Precedence” section. Updated “Related Policies” section to reflect Early Childhood Developmental Disorders medical policy (fka: Autism Spectrum Disorder, Coverage of Services).” Audit Information section added.

08/2015 Adopted BCBSA policy# 2.04.59

Health Care Procedure Coding System (HCPCS) codes related to chemotherapy drugs, drugs administered other than oral method, and enteral/parenteral formulas may be subject to National Drug Code (NDC) processing and pricing. The use of NDC on medical claims helps facilitate more accurate payment and better management of drug costs based on what was dispensed and may be required for payment. For more information on BCBSVT requirements for billing of NDC please refer to the provider portal http://www.bcbsvt.com/provider-home latest news and communications.

Approved by BCBSVT Medical Directors Date Approved

Joshua Plavin, MD
Senior Medical Director
Chair, Medical Policy Committee

Robert Wheeler MD
Chief Medical Officer

Attachment I
CPT & HCPCS Code List & Instructions

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Number</th>
<th>Description</th>
<th>Policy Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of</td>
<td>Prior Approval Required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
<td></td>
</tr>
</tbody>
</table>

The following codes are considered as medically necessary when applicable criteria have been met.
<table>
<thead>
<tr>
<th>CPT</th>
<th>81229</th>
<th>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</th>
<th>PRIOR APPROVAL REQUIRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<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>
<td>PRIOR APPROVAL REQUIRED</td>
</tr>
<tr>
<td>CPT</td>
<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>
<td>PRIOR APPROVAL REQUIRED</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S3870</td>
<td>Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability</td>
<td>PRIOR APPROVAL REQUIRED</td>
</tr>
</tbody>
</table>

**Type of Service:** Laboratory  
**Place of Service:** Outpatient  
**101315RLG**
## ICD-10 List

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The following diagnoses are considered medically necessary when applicable criteria is met.</td>
</tr>
<tr>
<td>F70</td>
<td>Mild intellectual disabilities</td>
</tr>
<tr>
<td>F71</td>
<td>Moderate intellectual disabilities</td>
</tr>
<tr>
<td>F72</td>
<td>Severe intellectual disabilities</td>
</tr>
<tr>
<td>F73</td>
<td>Profound intellectual disabilities</td>
</tr>
<tr>
<td>F78</td>
<td>Other intellectual disabilities</td>
</tr>
<tr>
<td>F79</td>
<td>Unspecified intellectual disabilities</td>
</tr>
<tr>
<td>F80.0</td>
<td>Expressive language disorder</td>
</tr>
<tr>
<td>F80.2</td>
<td>Mixed receptive-expressive language disorder</td>
</tr>
<tr>
<td>F80.4</td>
<td>Speech and language development delay due to hearing loss</td>
</tr>
<tr>
<td>F80.81</td>
<td>Childhood onset fluency disorder</td>
</tr>
<tr>
<td>F80.89</td>
<td>Other developmental disorders of speech and language</td>
</tr>
<tr>
<td>F80.9</td>
<td>Developmental disorder of speech and language, unspecified</td>
</tr>
<tr>
<td>F81.0</td>
<td>Specific reading disorder</td>
</tr>
<tr>
<td>F81.2</td>
<td>Mathematics disorder</td>
</tr>
<tr>
<td>F81.81</td>
<td>Disorder of written expression</td>
</tr>
<tr>
<td>F81.89</td>
<td>Other developmental disorders of scholastic skills</td>
</tr>
<tr>
<td>F81.9</td>
<td>Developmental disorder of scholastic skills, unspecified</td>
</tr>
<tr>
<td>F82</td>
<td>Specific developmental disorder of motor function</td>
</tr>
<tr>
<td>F84.0</td>
<td>Autistic Disorder</td>
</tr>
<tr>
<td>F88</td>
<td>Other disorders of psychological development</td>
</tr>
<tr>
<td>F89</td>
<td>Unspecified disorder of psychological development</td>
</tr>
<tr>
<td>H93.25</td>
<td>Central auditory processing disorder</td>
</tr>
<tr>
<td>R48.0</td>
<td>Dyslexia and alexia</td>
</tr>
</tbody>
</table>

101315RLG