# Medical Policy

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# Title: Genetic Testing - Chromosomal Microarray (CMA) Analysis and Next-Generation Sequencing Panels, for the Evaluation of Children with Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and/or Congenital Anomalies

## Description/Background

### DIAGNOSTIC TESTING

#### Karyotyping and Fluorescent In Situ Hybridization

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 autism spectrum disorder (ASD) but more often reflect normal genetic variation.[1] However, de novo CNVs are observed about 4 times more frequently in children with ASD than in normal individuals.[2] Less frequently, other abnormalities such as balanced translocations (i.e., 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 (Mb) in size, although standard G-banding evaluates more than 10-Mb changes. In children with DD/ID, a review by Stankiewicz and Beaudet (2007) found G-banded karyotyping diagnostic in approximately 3% to 5%.[3] In ASD, high-resolution karyotyping appears to identify abnormalities in up to 5% of cases.[4]

In contrast, molecular cytogenetic techniques can detect small submicroscopic chromosomal alterations. Fluorescent in situ hybridization (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,[5] diagnostic in approximately 5% to 6% of those with negative karyotypes, but uncommonly in ASD.[6]

**Chromosomal Microarrays**

Two types of CMAs are considered here: array comparative genomic hybridization (aCGH) and single nucleotide variants (SNV) 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 additional genomic material within that genomic location (e.g., a duplication), the sequence imbalance is detected as a difference in fluorescence intensity (Korf and Rehm [2013][7] offer an illustrative graphic). 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 florescent dyes. Comparative florescence 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 (UPD) or consanguinity. UPD occurs when a child 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.

Table 1 summarizes the cytogenetic tests used to evaluate children with DD/ID and autism. The table emphasizes the large difference in resolution between karyotyping and CMA.

**Table 1. Resolution and Analysis Comparison of FISH, Karyotyping, and CMA Analysis**

| Test | Resolution in Kilobases[a] | Analysis |
|---|---|---|
| Karyotyping | 3000-5000 kb | Genome-wide |
| CMA | ≈50 kb | Genome-wide |
| FISH | ≈500 to 1000 kb (depending on probe) | Targeted |

CMA: chromosomal microarray; FISH: fluorescent in situ hybridization; kb: kilobases.
[a] One kb= 1000 bases, 1000 kb= 1 Mb

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.[8]

### 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 sizes—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 DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY AND AUTISM SPECTRUM DISORDER

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 (e.g., “trio” testing of affected child, father, and mother) can identify an inherited CNV from an unaffected parent and therefore considered benign.[9] 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 (e.g., DECIPHER [https://decipher.sanger.ac.uk], ClinVar [http://www.ncbi.nlm.nih.gov/clinvar/]). 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.[10] 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.

The American College of Medical Genetics (ACMG) has published guidelines for evaluating, interpreting, and reporting pathogenicity reflecting these principles.[11] 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 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.”[12] The proposal defined levels of evidence describe how well or how poorly detected variants or CNVs correlate with phenotype.

## Regulatory Status

CMA analysis and NGS is commercially available from several laboratories as a laboratory-developed test. Laboratory-developed tests performed by laboratories licensed for high complexity testing under the Clinical Laboratory Improvement Amendments (CLIA) do not require U.S. Food and Drug Administration (FDA) clearance for marketing.

In July 2010, the FDA indicated that the agency would require microarray manufacturers to seek clearance in order to sell their products for use in clinical cytogenetics.

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

On January 17, 2014, the FDA cleared the Affymetrix CytoScan® Dx Assay for marketing. The FDA reviewed the Affymetrix CytoScan Dx Assay through its de novo classification process. For the de novo petition, the review of the CytoScan Dx Assay included an analytic evaluation of the test's ability to accurately detect numerous chromosomal variations of different types, sizes, and genome locations when compared with several analytically validated test methods. The 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

FirstStep$^{Dx}$ 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. The 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) designed for diagnosing 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 assesses 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**
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. Fulgent Genetics offers an next-generation sequencing ASD panel that includes 121 genes.

## Medical Policy Statement

The safety and effectiveness of chromosomal microarray analysis have been established. It may be considered a useful diagnostic option when indicated for patients meeting specific patient selection criteria.

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## Inclusionary and Exclusionary Guidelines

**Inclusions:**
Chromosomal microarray analysis may be considered established as first line testing in the initial postnatal evaluation of individual 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

**Exclusions:**

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

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## CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

***Established codes:***

S3870 81228 81229 81349

***Other codes (investigational, not medically necessary, etc.):***

81470 81471 0156U 0170U 0209U 0318U

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## Rationale

This review has been informed by a TEC Special Report (2009) on array comparative genomic hybridization (aCGH)[13] and a TEC Special Report (2015) on chromosomal microarray (CMA) testing for the genetic evaluation of patients with global developmental delay (DD), intellectual disability (ID), and autism spectrum disorder (ASD).[14]

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful.

Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Developmental Delay/Intellectual Disability**

Developmental delay (DD) is diagnosed in children five years or younger who show a significant delay in two or more developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living.[15] DD can precede the development of intellectual disability (ID) as the child ages.[16]

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 lifelong. 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 (e.g., IQ <70 or 75) that impact adaptive functioning in the conceptual, social, and practical domains.[17]

The national prevalence of developmental delay and intellectual disability were estimated at 4.1% and 1.2%, respectively, in US children based on data from the 2009 to 2017 National Health Interview Survey. [18] 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.[19] 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.[20] With the 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 ( for skilled specialists, as much as 20% to 40% of cases) without genetic testing.[21] The recommended approach to evaluation in DD/ID begins with 3-generation family history and physical (including neurologic) exam. Subsequent testing is used to confirm a suspected diagnosis (e.g., targeted fluorescent in situ hybridization [FISH] testing for DiGeorge or cri-du-chat syndromes). If no diagnosis is suspected, fragile X syndrome testing, metabolic testing for inborn errors of metabolism, and CMA testing (without karyotyping) are recommended, regardless of the presence or absence of dysmorphologic features or congenital anomalies.[15]

**Autism Spectrum Disorder**

DSM-5 definesASD15,[a] as the presence of:[17]

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

The estimated prevalence of ASD in US children based on data from the 2009 to 2017 National Health Interview Survey was 2.5%. [18] ASD is four to five 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 two. The evaluation includes developmental screening and diagnostic evaluation (i.e., hearing, vision, and neurologic testing; 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%.[2] A family with an affected child has a 13% to 19% risk for recurrence in subsequent children.[22] Based on Swedish genetic studies, Gaugler et al (2014) concluded that "the bulk of autism arises from genetic variation" (as opposed to environmental causes).[23] Still, although genetic determinants can be heritable, most appear to arise de novo.[2]

For these reasons, a child with ASD is often evaluated with genetic testing. Testing may be targeted when a child has a recognizable syndrome such as those shown in Table 2. Alternatively, high-resolution cytogenetic analysis evaluating multiple genes-the focus of this evidence review-is used.

**Table 2. Examples of Specific Genes Associated With Disorders That Include Autistic Behaviors**

| Gene (Syndrome) | Patient Selection | Yield, % | Reference |
|---|---|---|---|
| FMR1 (fragile X) | Unselected autism | 3-10 | Schaefer and Mendelsohn (2008)[24] |
| MECP2 (Rett) | Females with nonsyndromic autism, intellectual disability, and cerebral palsy | 3-13 | |
| PTEN | Autism with macrocephaly | ≤17 | Butler et al (2005)[25] |

[a] http://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd/index.shtml.[15]

## CHROMOSOMAL MICROARRAY TESTING

### Clinical Context and Test Purpose

The purpose of CMA testing is to identify a genetic cause for individuals with DD/ID, ASD, and congenital anomalies. A genetic diagnosis may end a diagnostic odyssey, improve treatment, facilitate the management of associated medical conditions, and permit carrier testing to assess risks to future offspring.

The following PICO was used to select literature to inform this review.

### Populations

The relevant population of interest includes patients with DD/ID, ASD, and congenital anomalies for whom the cause of the disorder has not been identified despite other established methods such as karyotyping.

### Interventions

The intervention of interest is CMA testing. Referral for genetic counseling is important for the explanation of the genetic disease, heritability, genetic risk, test performance, and possible outcomes.

### Comparators

The following practice is currently being used to diagnose DD/ID, ASD, and congenital anomalies: karyotyping. Karyotyping is typically administered in a tertiary care setting. Referral

for genetic counseling is important for the explanation of the genetic disease, heritability, genetic risk, test performance, and possible outcomes.

**Outcomes**
The potential beneficial outcomes of interest are diagnostic yield with avoidance of future testing, changes in management that lead to an improvement in health outcomes, and identification of unaffected carriers.

Potential harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to an incorrect diagnosis and inappropriate treatment. False-negative test results can lead to the absence of appropriate treatment and continuation of the diagnostic odyssey.

Follow-up to monitor for outcomes varies from immediately after testing diagnosis to long-term health outcomes subsequent to management changes

**Study Selection Criteria**
For the evaluation of clinical validity of the CMA test, studies that met the following eligibility criteria were considered: case series or cohort studies that enrolled 20 or more patients with clinical diagnoses DD/ID or ASD with known or suspicion of genetic abnormalities, with or without negative results by conventional cytogenetic evaluation, and performed CMA testing on enrolled patients. Studies were also included if they examined management decisions and/or patient outcomes based on genetic evaluation results.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Case Series or Cohort Studies**
Several studies have conducted CMA testing on samples with known chromosomal abnormalities using standard karyotyping and are summarized in Table 3. The median diagnostic yield in DD/ID patients from 21 studies published after 2012 was 19%. Most studies included patients with prior normal studies (e.g., karyotype and FMR1 testing). However, it is difficult to assess phenotype severity across studies owing to reporting and how samples were assembled. For a recent comparison, investigators reported diagnostic yield from 1133 children enrolled in the U.K. Deciphering Developmental Disorders study for whom a diagnosis was not established prior to CMA testing.[26] Using both CMA and exome sequencing, a diagnostic yield of 27% was achieved.

**Table 3. Diagnostic Yield of 67 Case Series Assessing Chromosomal Microarray Testing for DD, ID, and ASD Published Before 2015**

| Study | N | Diagnosis | Patient Description | Previous Normal Studies | Yield, % |
|---|---|---|---|---|---|
| Eriksson et al (2015)[27] | 162 | ASD | Suspected ASD | Karyotype (unclear precise proportion but < half) | 8.6 |
| Lay-Son et al (2015)[28] | 40 | DD/ID/Other | Patients had at least 2 of the following: Cas, facial dysmorphism, DD/ID | Karyotype, 4 (10%) patients had abnormality on karyotype but it did not convey a definite cause of patients disorder | 25.0 |
| Bartnik et al (2014a)[29] | 256 | DD/ID | DD/ID with or without dysmorphic features, additional neurodevelopmental abnormalities, and/or CA | G-banded karyotype, fragile X testing | 27.0 |
| Bartnik et al (2014b)[30] | 112 | DD/ID | ID accompanied by dysmorphic features and/or CA | G-banded karyotype, fragile X testing, MPLA | 21.4 |
| Chong et al (2014)[31] | 115 | DD/ID/ASD/CA | 105 patients with DD/ID/ASD/CA recruited by clinical genetics services | Karyotype | 19.0 |
| D'Amours et al (2014)[32] | 21 | CA | DD/ID with or without CA | Karyotype | 14.3 |
| Henderson et al (2014)[33] | 1780 | DD/ID/ASD | Referral to laboratory for CMA | Not specified | 12.7 |
| Nava et al (2014)[34] | 194 | ASD | ASD | Karyotype, fragile X testing, FISH | 1.5 |
| Nicholl et al (2014)[35] | 1700 | DD/ID/ASD | 1453 unrelated patients prospectively referred for investigation of DD/ID/ASD and 247 epilepsy cases | Uncertain | 11.5 |
| Palmer et al (2014)[36] | 67 | ID | Idiopathic ID | Karyotype, fragile X, subtelomeric MPLA | 19.0 |
| Preiksaitiene et al (2014)[37] | 211 | DD/ID | Syndromic and nonsyndromic cases of unknow etiology of DD/ID | FISH, MLPA, or karyotype | 13.7 |
| Redin et al (2014)[38] | 106 | DD/ID | Idiopathic ID | Karyotype | 24.5 |
| Roberts et al (2014)[39] | 215 | DD/ID/ASD | ID/ASD | Uncertain | 14.9 |
| Stobbe et al (2014)[40] | 23 | ASD | Retrospective review of patients referred for autism testing | Karyotype (<44% patient, 1 patient with known chromosomal abnormality | 21.7 |
| Tao et al (2014)[41] | 327 | DD/ID/ASD | Patients seen by clinical geneticist | Not specified | 11.3 |
| Utine et al (2014)[42] | 100 | ID | Idiopathic ID | Karyotype, FISH | 12.0 |
| Uwineza et al (2014)[43] | 50 | DD/ID | DD/ID/MCA | Karyotype | 26.0 |
| Battaglia et al (2013)[44] | 349 | DD/ID/ASD | Idiopathic DD/ID/ASD or dysmorphia | FISH or karyotype | 22.1 |

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|---|---|---|---|---|---|
| Lee et al (2013)[45] | 190 | DD/ID | Retrospective chart review of patients at single-center with idiopathic DD/ID | G-banded karyotype | 13.7 |
| Shoukier et al (2013)[46] | 342 | DD/ID | Retrospective review of idiopathic DD/ID | Karyotype | 13.2 |
| Sorte et al (2013)[47] | 50 | ASD | ASD | G-banded karyotype | 16.0 |
| Filges et al (2012)[48] | 131 | DD/ID/ASD | Consecutive patients with normal karyotype but presenting with chromosomal phenotypes: malformation syndromes, syndromic and nonsyndromic ID, and ASD | Karyotype | |
| Iourov et al (2012)[49] | 54 | ID/ASD/CA | Highly selected patients from group of 2426 patients based on clinical and cytogenic data | G-banded karyotype | 28.0 |
| McGrew et al (2012)[50] | 97 | ASD | Retrospective review of EMR for patients with ASD or pervasive DD NOS | Uncertain (karyotype?) | 6.2 |
| Tzetis et al (2012)[51] | 334 | DD/ID/ASD | DD/ID/ASD or with major CA or dysmorphic features | Karyotype, FISH, fragile X and Rett syndromes | 25.1 |
| Bremer et al (2011)[52] | 223 | ASD | 151 diagnosed ASD with normal Karyotype, 1 nonpathogenic inherited balanced translocation, 72 patients who had not received karyotyping | Karytype | 8.1 |
| Coulter et al (2011)[53] | 1792 | DD/ID/ASD | DD/ID/ASD, CA, dysmorphic features, seizures, hypotonia | Majority karyotype | 7.3 |
| Wincent et al (2011)[54] | 160 | DD/CA | Idiopathic DD/CA | Karyotype, fragile X, FISH, MPLA | 13.1 |
| Manolakos et al (2010)[55] | 82 | ID | Idiopathic MR | G-banded karyotype | 3.6 |
| Rosenfeld et al (2010)[56] | 1461 | ASD | Retrospective review of putative ASD submitted for clinical testing | Not specified | 7.7 |
| Schaefer et al (2010)[57] | 68 | ASD | Retrospective review of patients who had received aCGH for autism | Uncertain | 22.0 |
| Shen et al (2010)[58] | 848 | ASD | Idiopathic MR and/or dysmorphism or MCAs | G-banded karyotype, fragile X | 7.0 |
| Bruno et al (2009)[59] | 117 | DD/ID | Idiopathic MR and/or CA | Karyotype (400 to 650-band level) | 15.4 |
| Friedman et al (2009)[60] | 100 | ID | Moderate-to-severe idiopathic DD/MR with CA | Uncertain | 16.0 |
| Baldwin et al (2008)[61] | 211 | DD/ID/ASD | Various, including idiopathic DD/ID, dysmorphic features, CA, ASD, or syndromal phenotype | G-banded karyotype (many) | 15.6 |
| Christian et al (2008)[62] | 397 | ASD | Nonsyndromic autism, subset of AGRE subjects (Roswell Park Cancer Institute) | Karyotype | 11.6 |
| Marshall et al (2008)[63] | 427 | ASD | ASD | Karyotype (32 with known abnormality) | 6.3 |

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|---|---|---|---|---|---|
| Pickering et al (2008)[64] | 1176 | DD/ID/CA | Consecutive cases referred for idiopathic DD/MR/MCA or other dysmorphia | Karyotype (30 with visible chromosomal abnormality), FISH in some patients | 9.8 |
| Saam et al (2008)[65] | 490 | DD/ID | DD/ID | Karyotype | 17.6 |
| Shevell et al (2008)[66] | 94 | DD/ID | DD | G-banded karyotype, fragile X, FMR1, neuroimaging | 6.4 |
| Aradhya et al (2007a)[67] | 20 | DD/ID | DD/ID and either dysmorphic features, CA, or growth retardation | G-banded karyotype, FISH | 30.0 |
| Aradhya et al (2007b)[67] | 20 | DD/ID | As above | As above | 50.0 |
| Ballif et al (2007)[68] | 6946 | DD/ID | Various clinical presentations, most commonly DD, dysmorphic features, and/or MCA | Karyotype, subtelomere FISH | 2.4 |
| Froyen et al (2007)[69] | 108 | DD/ID | Suspicious for X-linked MR | G-banded karyotype, FMR1 | 13.0 |
| Hoyer et al (2007)[70] | 104 | DD/ID | Unselected patients with idiopathic MR | G-banded karyotype | 9.1 |
| Lu et al (2007)[71] | 1726 | DD/ID | DD/ID, dysmorphic, or MCA features | G-banded karyotype and/or FISH | 5.2 |
| Madrigal et al (2007)[72] | 54 | DD/ID | Idiopathic MR; 52 from families with X-linked inherited MR; 2 with suspicion of X chromosome deletion | Karyotype, FMR1 | 11.6 |
| Sebat et al (2007)[73] | 195 | ASD | Nonsyndromic autism; majority from AGRE or NIMH Center for Collaborative Genetic Studies on Mental Disorders | Karyotype | 7.2 |
| Shen et al (2007)[74] | 211 | DD/ID | ASD | Not selected by prior results | 8.1 |
| Thuresson et al (2007)[75] | 48 | DD/ID | Idiopathic MR and CA | G-banded karyotype, subtelomere FISH | 6.0 |
| Wagenstaller et al (2007)[76] | 67 | DD/ID | Idiopathic MR | G-banded karyotype, FISH (n=42) | 16.4 |
| Ballif et al (2006)[77] | 3600 | DD/ID | Consecutive cases with diverse range of DD or MR features | Not specified | 5.1 |
| Friedman et al (2006)[78] | 100 | DD/ID | Idiopathic ID | Karyotype | 11.0 |
| Jacquemont et al (2006)[79] | 29 | ASD | Syndromic ASD | Karyotype, biochemical tests | 28.0 |
| Krepischi-Santos et al (2006)[28] | 95 | DD/ID | Syndromic MR or other | G-banded karyotype, FMR1 (in some) | 15.8 |
| Lugtenberg et al (2006)[80] | 40 | DD/ID | Idiopathic MR, suspicious for X-linked abnormality | Karyotype | 7.5 |
| Menten et al (2006)[81] | 140 | DD/ID | Idiopathic MR and MCA | Karyotype, subtelomere MPLA (n=31) | 13.6 |
| Miyake et al (2006)[82] | 30 | DD/ID | Idiopathic MR with some dysmorphic features | G-banded karyotype | 16.7 |
| Rosenberg et al (2006)[83] | 81 | DD/ID | Idiopathic MR and CA | Karyotype | 16.0 |

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|---|---|---|---|---|---|
| Shaffer et al (2006)[84] | 1500 | DD/ID | Consecutive patients with DD or MR | Karyotype (94%), FISH (20%) where prior testing available | 5.6 |
| Sharp et al (2006)[85] | 290 | DD/ID | Idiopathic MR with or without dysmorphism or MCA | Karyotype, subtelomere FISH (n=255) | 5.5 |
| De Vries et al (2005)[86] | 100 | DD/ID | Idiopathic MR | G-banded karyotype, subtelomere MPLA | 10.0 |
| Schoumans et al (2005)[87] | 41 | DD/ID | Mild-to-severe idiopathic MR and dysmorphism and/or family history; patients scored >3 on de Vries checklist (2001) | Spectral karyotype (n=11), subtelomere FISH (n=30) | 9.8 |
| Tyson et al (2005)[88] | 22 | DD/ID | Mild-to-moderate MR and nonsyndromic dysmorphic features; patients scored >3 on de Vries checklist (2001) | G-banded karyotype, subtelomere FISH (n=13) | 13.6 |
| Harada et al (2004)[89] | 69 | DD/ID | Idiopathic MR, with or without MCA | Karyotype (400-band level) | 5.8 |
| Shaw-Smith et al (2004)[90] | 50 | DD/ID | Idiopathic MR and dysmorphism or other features | Karyotype, subtelomere (n=41) | 14.0 |
| Vissers et al (2003)[91] | 20 | DD/ID | Idiopathic MR and dysmorphism; patients scored >3 on de Vries checklist (2001) | Karyotype | 10.0 |

aCGH:array comparative genomic hybridization; AGRE: Autism Genetic Resource Exchange; ASD: autism spectrum disorder; CA: congenital anomaly; DD: developmental delay; EMR: electronic medical records; FISH: fluorescent in situ hybridization; EMR: electronic medical record; FISH: fluorescent in situ hybridization; ID: intellectual disability; MCA: multiple congenital anomalies; MPLA: ligation-dependent probe amplification; MR: mental retardation; NIMH: National Institute of Mental Health

Six additional studies published after 2015 are summarized in Table 4.[92,93,94,95,96] In the first study by Ho et al (2016), the overall detection rate of copy number variant (CNVs) was 29.4 (9.2% pathogenic, 20.2% variant of uncertain significance) in 5487 patients.[96] In the second study by Ho et al (2016), the overall detection rate of CNVs was 28.1% (8.6% pathogenic, 19.4% variant of uncertain significance) in 10,351 consecutive patients, with an average of 1.2 reportable CNVs per individual.[97] Overlap of patients in the 2 reports is unclear.

**Table 4. Diagnostic Yield of Studies of Patients With DD, ID, and ASD Published After 2015**

| Study | N | Diagnoses | Patient Description | Previous Normal Studies | Yield, % |
|---|---|---|---|---|---|
| Chaves et al (2019)[92,] | 420 | DD/ID/facial dysmorphism/ASD | Children in Brazil with neurodevelopment disorders (62% male; mean age, 9.5 y; range 0 to 49 y) | Karotype (n=138) | 18 (all) |
| Hu et al (2019)[93] | 633 | DD/ID/ASD | Children in China with DD/ID/ASD (359 males, 274 females; age range, 3 mo to 17 y) | Uncertain | 20.06 (all) |
| Xu et al (2018)[94,] | 434 | DD/ID/ASD | Children in China with DD/ID/ ASD (371 boys, 63 girls; mean age, 6 y; range, 4 mo to 17 y) | Uncertain | 13.6 (all)<br>14.7 (excluding ASD) 12 (only ASD) |

| | | | | | |
|---|---|---|---|---|---|
| Sansovic et al (2017)[95] | 337 | DD/ID/ASD or CAs | Children in Croatia with DD/ID/ASD or CA (median age, 7 y; range, 1 mo to 25 y) | Some patients had previous classical cytogenetic and molecular cytogenetic methods | 21.6 (all) |
| Ho et al (2016)[96], | 5487 | DD/ID/ASD | DD/ID/ASD with or without multiple CAs, speech/language delay | Uncertain | 29.4 (all)<br>33 (excluding ASD)<br>25 (only ASD) |
| Ho et al (2016)[97], | 10,351 | DD/ID/ASD or multiple CAs | DD/ID/ASD or multiple CAs | Uncertain | 28.1 (all)<br>33 (excluding ASD)<br>24.4 (only ASD) |

ASD: autism spectrum disorder; CA: congenital anomaly; DD: developmental delay; ID: intellectual disability.

Studies that reported on diagnostic yield for congenital anomalies are summarized in Table 5. No studies were identified that evaluated diagnostic yield of CMA for idiopathic language delay.

**Table 5. Diagnostic Yield Studies in Patients With Congenital Anomalies**

| Study | N | Diagnoses | Patient Description | Previous Normal Studies | Yield |
|---|---|---|---|---|---|
| Hu et al (2016)[98] | 119 | Idiopathic short stature | Height of the individual is below 2 SDS of the corresponding mean height for a given age, sex, and population group, and no known causes can be found | Uncertain | 3/119 (2.5%) identified with a pathogenic CNV |
| Lu et al (2008)[99] | 638 | Birth defects | Neonates with possible chromosomal abnormality, ambiguous genitalia, dysmorphic features, multiple congenital anomalies, congenital heart disease | Uncertain | 109 (17.1%) patients were identified with clinically significant CNVs most of which would not have been defined by karyotyping |

CNV: copy number variant; SDS: standard deviation score.

## Clinical Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

As noted, CMA testing has a higher diagnostic yield than standard karyotyping, which is an accepted test in the evaluation of DD/ID, ASD, and congenital anomalies. In some cases, disorders are defined by the presence of a genetic variant or genetic testing can contribute to the diagnosis.

In some cases, a specific diagnosis leads to management changes that are either standard of care or are likely to lead to improvements in outcomes.

**Changes in Management**
A reasonable body of literature has evaluated whether or not the establishment of a definitive diagnosis in patients with DD/ID, ASD, and/or congenital anomalies leads to changes in management that are likely to improve outcomes. Of particular interest in the use of CMA testing to make a specific genetic diagnosis in a patient with DD/ID, ASD, and/or congenital anomalies is the effect of that diagnosis on the patient's family. Because many affected patients will be evaluated for testing in childhood, the implications of testing on family members and the reciprocal effect on the patient are considerations.

Results of six retrospective studies that examined the potential impact of CMA results on clinical decisions are summarized in Table 8. These studies 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 cited by parents[100] and noted as an outcome in case series and reports.[101] For example, Turner et al (2008) found a median of 16.5 years from the initial medical contact to identify a causal variant in 38 extended families with fragile X syndrome.[102] Saam et al (2008) noted that CMA testing may influence that odyssey.[65] Parents cite obtaining services and support as a reason for testing but how the frequency can impact 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 studies following children at presentation to final outcomes. In addition to these studies, Lingen et al (2016) has reported a benefit for maternal quality of life if aCGH tests succeed to clarify the etiologic diagnosis in an affected child.[103]

**Table 6. Studies Reporting Management Changes After CMA Testing**

| Study | Dates Testing | Patients (Tests) | Diagnostic Yield, n (%) or % | Pathogenic, n | Actionable, n (%) | Clinical Management Changes, n (%) |
|---|---|---|---|---|---|---|
| Hayeems et al (2015)[104] | 2009-2011 | 752 (Dd and/or CA) | 114 (15.2)[f]<br>72 (9.6)[g] | 114 | • 79.6% (364/457) with reportable results<br>• 62.4% (184/295) with benign results received medical recommendations | • Specialist consults: 221 (37.7)<br>• Imaging: 125 (21.3)<br>• Lab tests: 70 (12.0)<br>• Surveillance: 88(15.0)<br>• Family: 82(14.0) |
| Henderson et al (2014)[33] | 2009-2012 | 1780 (DD/ID/ASD (81.5% of 227 abnormal) | 12.7 | 187 | 102 (54.5) | • Referral: 84(44.9)<br>• Screening: 11(5.9)<br>• Imaging: 38(20.3)<br>• Lab tests: 29(15.5) |
| Tao et al (2014)41 | 2011-2013 | 327 DD/ID/ASD | 11.3 | 9[e] | 6(66.7) | |
| Ellison et al (2012)[105] | 2004-2011 | 46,298 DD/ID dysmorphic, neurobehavioral others | 5.4 | 1259 | 441(35)[d] | Clinically actionable responses included additional specific tests for monitoring specific disorders |
| Coulter et al (2011)[53] | 2009-2010 | 1792 DD/ID/ASD or CA | 7.3[a]<br>5.8[b] | 121[a,c]<br>73[a,c] | 65(53.7)[a]<br>25 (34.2)[b] | • Referral: 67 (60)[a] and 11 (29)[b]<br>• Imaging: 25(22)[a] and 11(29)[b]<br>• Lab tests: 20(18)[a] and 18(47)[b] |
| Saam et al (2008)[65] | 2005-2007 | 490 DD/ID | 17.6 | 48 | 34(70.8) | • Referral: 7(14.6)<br>• Screening: 8(16.7)<br>• Avoid further genetic testing: 12(25)<br>• Improved access to services: 12(25) |

- Reproductive recurrence risk: 17(35.4)

ASD: autism spectrum disorder; CA: congenital anomaly; CMA: chromosomal microarray; DD: developmental delay; ID: intellectual disability.
[a] Abnormal.
[b] Possibly significant.
[c] Percentages as reported in the publication-denominators varied from 121 and 73.
[d] Assumed to be from pathogenic results oligonucleotide arrays.
[e] Of the 215 patients with DD/ID or ASD.
[f] Clinically significant.
[g] Uncertain, likely clinically significant.

### Reproductive Decision Making

Risk estimates for recurrence of disease in future births can be altered considerably by information from the genetic diagnosis (see Table 7). Having a child with ASD appears to impact reproductive decision-making or so-called reproductive stoppage. For example, Hoffmann et al (2014) examined reproductive stoppage in families with ASD using the California Department of Developmental Services database linked to birth certificates.106, Between 1990 and 2003, 19,710 families with 39,361 siblings and half-siblings were identified. Birth histories in these families were then compared with a control group (matched 2:1 by sex, birth year, maternal age, ethnicity/race, and county). Investigators found fertility rates in case and control families similar in the 2 years following the birth of a child with ASD, but, in the subsequent years, the rate was 33% (95% confidence interval, 30% to 37%) lower in families having a child affected by ASD.

**Table 7. Sibling Recurrence Risk After Identification of Different Types of Genomic Abnormalities Associated With ASD**

| Type of Genetic Abnormality | Clinical Example | Sibling Recurrence Risk |
|---|---|---|
| Dominant single-gene disorder with full penetrance | Tuberous sclerosis: involves abnormalities of the skin, brain, and heart; associated with ID and ASD | 50% if parent carries the disease-causing variant (ie, not a de novo variant) |
| Recessive single-gene disorder | Smith-Lemli-Opitz syndrome: congenital multiple anomaly syndrome; associated with ASD | 25% |
| X-linked single-gene disorder | Fragile X syndrome: most common cause of mental retardation; associated with ASD | Brother: 50%<br>Sister: up to 50% will be carriers or might be mildly affected |
| Copy number variant | Prader-Willi syndrome/Angelman syndrome (15q11-q13 duplication) | Same as population prevalence if de novo (ie, not found in parents) |

ASD: autism spectrum disorder; ID: intellectual disability.

### Section Summary: Chromosomal Microarray Testing

The evidence for CMA testing for a definitive diagnosis in individuals with DD/ID, ASD, and/or congenital anomalies consists of studies reporting on the yield of a positive test in affected individuals, combined with an indirect chain of evidence to support the clinical utility of testing. The yield of testing varies depending on the underlying population tested, but is generally higher than 10%, with higher rates in patients with congenital anomalies. While direct evidence of improved outcomes with CMA compared with karyotype is lacking, for at least a subset of the disorders potentially diagnosed with CMA in this patient population, there are well-defined and accepted management steps associated with positive test results. Further, there is evidence of changes in reproductive decision making as a result of positive test results. For children with idiopathic growth or language delay, clinical validity has not been established and there is no direct or indirect evidence to support clinical utility.

### NEXT-GENERATION SEQUENCING Panel Testing

### Clinical Context and Test Purpose

The purpose of gene panel testing with next generation sequencing (NGS) is to identify a genetic cause for individuals with DD/ID, ASD, and congenital anomalies. A genetic diagnosis may end a diagnostic odyssey, improve treatment, facilitate the management of associated medical conditions, and permit carrier testing to assess risks to future offspring.

The following PICO was used to select literature to inform this review.

### Populations

The relevant population of interest includes patients with DD/ID, ASD, and congenital anomalies for whom the cause of the disorder has not been identified despite other established methods such as karyotyping and CMA testing.

### Interventions

The relevant population of intervention of interest is gene panel testing with NGS. Next-generation sequencing testing is typically administered in a tertiary care setting. Referral for genetic counseling is important for the explanation of the genetic disease, heritability, genetic risk, test performance, and possible outcomes.

### Comparators

The following test is currently being used to diagnose developmental delay/intellectual disability, ASD, and congenital anomalies: CMA testing. CMA testing is typically administered in a tertiary care setting. Referral for genetic counseling is important for the explanation of the genetic disease, heritability, genetic risk, test performance, and possible outcomes.

### Outcomes

The potential beneficial outcomes of interest are the identification of a genetic bases of the disorder, avoidance of future testing, changes in management that lead to an improvement in health outcomes, and identification of unaffected carriers.

Potential harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to an incorrect diagnosis and inappropriate treatment. False-negative test results can lead to the absence of appropriate treatment and continuation of the diagnostic odyssey.

Follow-up to monitor for outcomes varies from immediately following testing to identify diagnostic accuracy to long-term health outcomes subsequent to management changes.

## Study Selection Criteria

For the evaluation of clinical validity of the gene panel testing with next-generation sequencing, studies that meet the following eligibility criteria were considered: case series or cohort studies that enrolled 20 or more patients with clinical diagnoses developmental delay/intellectual disability or ASD with known or suspicion of genetic abnormalities, with or without negative results by CMA testing on enrolled patients. Studies were also included if they examined management decisions and/or patient outcomes based on genetic evaluation results.

### Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

## Case Series or Cohort Studies

Several studies have assessed next-generation sequencing panel testing on samples from patients with intellectual disability with negative aCGH testing. Table 8 summarizes the diagnostic yield. For example, Grozeva et al (2016) reported that next-generation sequencing targeted testing resulted in an 11% additional diagnostic yield beyond the 10% to 15% yield from aCGH alone.[107,] However, Kalsner et al (2018) reported no increase in yield using an NGS panel.[108,]

**Table 8. Diagnostic Yield Studies Published**

| Study | N | Diagnoses | Patient Description | Previous Normal Studies | Yield |
|---|---|---|---|---|---|
| Kalsner et al (2018) [106,] | 100 | ASD | Consecutive children referred to a single U.S. neurogenetics clinic with confirmed diagnosis of ASD without a known genetic diagnosis suspected to be causative of ASD | Performed concurrently with CMA | CMA yield: 12% (included pathogenic CNVs and VUS) NGS panel yield: 11% (included pathogenic or likely pathogenic variants [VUS likely pathogenic]) |
| Grozeva et al (2015)[107,] | 986 | M-to-S ID | 996 patients with M-to-S ID from the U.K. (70%), Australia, Spain, U.S., and Italy. Studied phenotypes included: 905 cases with congenital heart disease; 911 cases with ciliopathy, coloboma, neuromuscular disease, severe insulin resistance, congenital thyroid disease. | Negative CMA testing at 500 kb resolution, and testing for fragile X and Prader-Willi or Angelman syndrome | 11% (likely pathogenic rare variant)· 8% (likely pathogenic· loss-of-function variant) 3% (known pathogenic missense variant) |
| Redin et al (2014)[38] | 166 | ID | ID patients with or without associated autistic-like features, fragile X, and other specific genetic conditions | Negative for aCGH | Overall diagnostic yield: 25%, with 26 causative variants (16 X-linked, 10 de novo in autosomal-dominant genes). |

aCGH: array comparative genomic hybridization; ASD: autism spectrum disorder; CHD: congenital heart disease; CMA: chromosomal microarray; CNV: copy number variant; ID: intellectual disability; M-to-S: moderate-to-severe; NGS: next-generation sequencing; VUS: variant of uncertain significance.

## Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No peer-reviewed, full-length randomized trials on the clinical utility of the commercially available next-generation sequencing panels for developmental delay/intellectual disability or ASD were identified.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Because the clinical validity of next-generation sequencing testing in these populations has not been established, a chain of evidence supporting the clinical utility of next-generation sequencing cannot be constructed.

**Section Summary: Next-Generation Sequencing**
It is arguable that the indirect chain of evidence for the use of CMA in evaluating DD/ID, ASD, and/or congenital anomalies would apply to NGS panels. However, the clinical validity of NGS panels is less well-established than for CMA, particularly regarding VOUS rates. 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. Therefore, the evidence does not permit conclusions whether NGS panel testing improves outcomes.

**SUMMARY OF EVIDENCE**
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 testing 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 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 next-generation sequencing 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 next-generation sequencing 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.

## SUPPLEMENTAL INFORMATION

### PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

**American Academy of Pediatrics (AAP)**

In 2014, the AAP issued a clinical report on the optimal medical genetics evaluation of a child with or global developmental delays (GDD) or ID.[15] Regarding CMA testing, this report states:

"CMA now should be considered a first tier diagnostic test in all children with GDD/ID for whom the causal diagnosis is not known…CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies."

In 2020, the AAP issued a clinical report on identifying infants and young children with developmental disorders through surveillance and screening. [115] The report proposed a screening model that included performing a complete medical evaluation and stated that a

"child with suspected global developmental delay or intellectual disability should have laboratory testing done, including chromosomal microarray and fragile X testing[...] Further testing may be indicated when a diagnosis is not established with initial laboratory evaluation including whole exome sequencing and gene panels."

**American Academy of Child and Adolescent Psychiatry**

In 2014, the American Academy of Child and Adolescent Psychiatry updated its guidelines on the assessment and treatment of children and adolescents with autism spectrum disorder (ASD).[109] The Academy recommended that "all children with ASD should have a medical assessment, which typically includes physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis, and genetic testing, which may include G-banded karyotype, fragile X testing, or chromosomal microarray."

**American Academy of Neurology and Child Neurology Society**

In 2011, the American Academy of Neurology and the Practice Committee of the Child Neurology Society updated their guideline regarding the evaluation of unexplained global developmental delay/intellectual disability with information on genetic and metabolic

(biochemical) testing in order to accommodate advances in the field.[110] The guidelines concluded that CMA testing has the highest diagnostic yield in children with DD/ID, ASD, or multiple congenital anomalies (MCA). 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) (2010; reaffirmed 2020) published guidelines on array-based technologies and their clinical utilization for detecting chromosomal abnormalities.[111, 112] Chromosomal microarray testing for copy number variation (CNV) is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

- Multiple anomalies not specific to a well-delineated genetic syndrome
- Apparently non-syndromic developmental delay/ intellectual disability
- Autism spectrum disorders (ASDs)

Other ACMG guidelines have addressed the design and performance expectations for clinical microarrays and associated software[8] and for the interpretation and reporting of CNVs,[11] both intended for the post-natal setting. A 2013 update includes recommendations for validation of microarray methodologies for both prenatal and postnatal specimens.[113]

A 2013 guidelines update from the 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 FXS [fragile X syndrome] and CMA, and second tier to include MECP2 and PTEN testing.[114] 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."

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this policy.

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## Government Regulations
## National:
No national coverage determination on this topic.

## Local:

No local coverage determination on this topic.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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## Related Policies

- Genetic Testing and Counseling
- Genetic testing for Tay-Sachs Disease
- Genetic Testing for Myotonic Dystrophy
- Genetic Testing for Cystic Fibrosis
- Genetic Testing for FMR1 and FMR2 Variants (Including Fragile X and Fragile XE Syndromes)
- Genetic Testing-Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise.

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## References


1. Mikhail FM, Lose EJ, Robin NH, et al. Clinically relevant single gene or intragenic deletions encompassing critical neurodevelopmental genes in patients with developmental delay, mental retardation, and/or autism spectrum disorders. Am J Med Genet A. Oct 2011; 155A(10): 2386-96. PMID 22031302
2. Brandler WM, Sebat J. From de novo mutations to personalized therapeutic interventions in autism. Annu Rev Med. 2015; 66: 487-507. PMID 25587659
3. Stankiewicz P, Beaudet AL. Use of array CGH in the evaluation of dysmorphology, malformations, developmental delay, and idiopathic mental retardation. Curr Opin Genet Dev. Jun 2007; 17(3): 182-92. PMID 17467974
4. Stuart SW, King CH, Pai GS. Autism spectrum disorder, Klinefelter syndrome, and chromosome 3p21.31 duplication: a case report. MedGenMed. Dec 18 2007; 9(4): 60. PMID 18311409
5. Moeschler JB. Medical genetics diagnostic evaluation of the child with global developmental delay or intellectual disability. Curr Opin Neurol. Apr 2008; 21(2): 117-22. PMID 18317267
6. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders. Genet Med. Apr 2008; 10(4): 301-5. PMID 18414214
7. Korf BR, Rehm HL. New approaches to molecular diagnosis. JAMA. Apr 10 2013; 309(14): 1511-21. PMID 23571590
8. Kearney HM, South ST, Wolff DJ, et al. American College of Medical Genetics recommendations for the design and performance expectations for clinical genomic copy number microarrays intended for use in the postnatal setting for detection of constitutional abnormalities. Genet Med. Jul 2011; 13(7): 676-9. PMID 21681105
9. Rodriguez-Revenga L, Vallespin E, Madrigal I, et al. A parallel study of different array-CGH platforms in a set of Spanish patients with developmental delay and intellectual disability. Gene. May 25 2013; 521(1): 82-6. PMID 23524024

10. Kloosterman WP, Hochstenbach R. Deciphering the pathogenic consequences of chromosomal aberrations in human genetic disease. Mol Cytogenet. 2014; 7(1): 100. PMID 25606056
11. Kearney HM, Thorland EC, Brown KK, et al. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. Genet Med. Jul 2011; 13(7): 680-5. PMID 21681106
12. Riggs ER, Church DM, Hanson K, et al. Towards an evidence-based process for the clinical interpretation of copy number variation. Clin Genet. May 2012; 81(5): 403-12. PMID 22097934
13. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). TEC Special Report: Array Comparative Genomic Hybridization (aCGH) for the Genetic Evaluation of Patients with Developmental Delay/Mental Retardation and Autism Spectrum Disorder. TEC Assessments. 2009;Volume 24;Tab 10.
14. Blue Cross and Blue Shield Association. Special Report: Chromosomal Microarray for the Genetic Evaluation of Patients With Global Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder. TEC Assessments. 2015;Volume 30;Tab 2.
15. Moeschler JB, Shevell M, Moeschler JB, et al. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics. Sep 2014; 134(3): e903-18. PMID 25157020
16. Shevell M, Ashwal S, Donley D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. Neurology. Feb 11 2003; 60(3): 367-80. PMID 12578916
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5. Washington (DC): American Psychiatric Association; 2013.
18. Zablotsky B, Black LI, Maenner MJ, et al. Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009-2017. Pediatrics. Oct 2019; 144(4). PMID 31558576
19. Srour M, Shevell M. Genetics and the investigation of developmental delay/intellectual disability. Arch Dis Child. Apr 2014; 99(4): 386-9. PMID 24344174
20. Willemsen MH, Kleefstra T. Making headway with genetic diagnostics of intellectual disabilities. Clin Genet. Feb 2014; 85(2): 101-10. PMID 23895455
21. Moeschler JB. Genetic evaluation of intellectual disabilities. Semin Pediatr Neurol. Mar 2008; 15(1): 2-9. PMID 18342255
22. Yuen RK, Thiruvahindrapuram B, Merico D, et al. Whole-genome sequencing of quartet families with autism spectrum disorder. Nat Med. Feb 2015; 21(2): 185-91. PMID 25621899
23. Gaugler T, Klei L, Sanders SJ, et al. Most genetic risk for autism resides with common variation. Nat Genet. Aug 2014; 46(8): 881-5. PMID 25038753
24. Schaefer GB, Mendelsohn NJ. Genetics evaluation for the etiologic diagnosis of autism spectrum disorders. Genet Med. Jan 2008; 10(1): 4-12. PMID 18197051
25. Butler MG, Dasouki MJ, Zhou XP, et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. J Med Genet. Apr 2005; 42(4): 318-21. PMID 15805158
26. Wright CF, Fitzgerald TW, Jones WD, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet. Apr 04 2015; 385(9975): 1305-14. PMID 25529582
27. Eriksson MA, Lieden A, Westerlund J, et al. Rare copy number variants are common in young children with autism spectrum disorder. Acta Paediatr. Jun 2015; 104(6): 610-8. PMID 25661985

28. Krepischi-Santos AC, Vianna-Morgante AM, Jehee FS, et al. Whole-genome array-CGH screening in undiagnosed syndromic patients: old syndromes revisited and new alterations. Cytogenet Genome Res. 2006; 115(3-4): 254-61. PMID 17124408
29. Bartnik M, Nowakowska B, Derwinska K, et al. Application of array comparative genomic hybridization in 256 patients with developmental delay or intellectual disability. J Appl Genet. Feb 2014; 55(1): 125-44. PMID 24297458
30. Bartnik M, Wisniowiecka-Kowalnik B, Nowakowska B, et al. The usefulness of array comparative genomic hybridization in clinical diagnostics of intellectual disability in children. Dev Period Med. Jul-Sep 2014; 18(3): 307-17. PMID 25182394
31. Chong WW, Lo IF, Lam ST, et al. Performance of chromosomal microarray for patients with intellectual disabilities/developmental delay, autism, and multiple congenital anomalies in a Chinese cohort. Mol Cytogenet. 2014; 7: 34. PMID 24926319
32. D'Amours G, Langlois M, Mathonnet G, et al. SNP arrays: comparing diagnostic yields for four platforms in children with developmental delay. BMC Med Genomics. Dec 24 2014; 7: 70. PMID 25539807
33. Henderson LB, Applegate CD, Wohler E, et al. The impact of chromosomal microarray on clinical management: a retrospective analysis. Genet Med. Sep 2014; 16(9): 657-64. PMID 24625444
34. Nava C, Keren B, Mignot C, et al. Prospective diagnostic analysis of copy number variants using SNP microarrays in individuals with autism spectrum disorders. Eur J Hum Genet. Jan 2014; 22(1): 71-8. PMID 23632794
35. Nicholl J, Waters W, Mulley JC, et al. Cognitive deficit and autism spectrum disorders: prospective diagnosis by array CGH. Pathology. Jan 2014; 46(1): 41-5. PMID 24300712
36. Palmer E, Speirs H, Taylor PJ, et al. Changing interpretation of chromosomal microarray over time in a community cohort with intellectual disability. Am J Med Genet A. Feb 2014; 164A(2): 377-85. PMID 24311194
37. Preiksaitiene E, Molyte A, Kasnauskiene J, et al. Considering specific clinical features as evidence of pathogenic copy number variants. J Appl Genet. May 2014; 55(2): 189-96. PMID 24535828
38. Redin C, Gerard B, Lauer J, et al. Efficient strategy for the molecular diagnosis of intellectual disability using targeted high-throughput sequencing. J Med Genet. Nov 2014; 51(11): 724-36. PMID 25167861
39. Roberts JL, Hovanes K, Dasouki M, et al. Chromosomal microarray analysis of consecutive individuals with autism spectrum disorders or learning disability presenting for genetic services. Gene. Feb 01 2014; 535(1): 70-8. PMID 24188901
40. Stobbe G, Liu Y, Wu R, et al. Diagnostic yield of array comparative genomic hybridization in adults with autism spectrum disorders. Genet Med. Jan 2014; 16(1): 70-7. PMID 23765050
41. Tao VQ, Chan KY, Chu YW, et al. The clinical impact of chromosomal microarray on paediatric care in Hong Kong. PLoS One. 2014; 9(10): e109629. PMID 25333781
42. Utine GE, Haliloglu G, Volkan-Salanci B, et al. Etiological yield of SNP microarrays in idiopathic intellectual disability. Eur J Paediatr Neurol. May 2014; 18(3): 327-37. PMID 24508361
43. Uwineza A, Caberg JH, Hitayezu J, et al. Array-CGH analysis in Rwandan patients presenting development delay/intellectual disability with multiple congenital anomalies. BMC Med Genet. Jul 12 2014; 15: 79. PMID 25016475
44. Battaglia A, Doccini V, Bernardini L, et al. Confirmation of chromosomal microarray as a first-tier clinical diagnostic test for individuals with developmental delay, intellectual disability, autism spectrum disorders and dysmorphic features. Eur J Paediatr Neurol. Nov 2013; 17(6): 589-99. PMID 23711909

45. Lee CG, Park SJ, Yun JN, et al. Array-based comparative genomic hybridization in 190 Korean patients with developmental delay and/or intellectual disability: a single tertiary care university center study. Yonsei Med J. Nov 2013; 54(6): 1463-70. PMID 24142652
46. Shoukier M, Klein N, Auber B, et al. Array CGH in patients with developmental delay or intellectual disability: are there phenotypic clues to pathogenic copy number variants?. Clin Genet. Jan 2013; 83(1): 53-65. PMID 22283495
47. Sorte HS, Gjevik E, Sponheim E, et al. Copy number variation findings among 50 children and adolescents with autism spectrum disorder. Psychiatr Genet. Apr 2013; 23(2): 61-9. PMID 23277134
48. Filges I, Suda L, Weber P, et al. High resolution array in the clinical approach to chromosomal phenotypes. Gene. Mar 10 2012; 495(2): 163-9. PMID 22240311
49. Iourov IY, Vorsanova SG, Kurinnaia OS, et al. Molecular karyotyping by array CGH in a Russian cohort of children with intellectual disability, autism, epilepsy and congenital anomalies. Mol Cytogenet. Dec 31 2012; 5(1): 46. PMID 23272938
50. McGrew SG, Peters BR, Crittendon JA, et al. Diagnostic yield of chromosomal microarray analysis in an autism primary care practice: which guidelines to implement?. J Autism Dev Disord. Aug 2012; 42(8): 1582-91. PMID 22089167
51. Tzetis M, Kitsiou-Tzeli S, Frysira H, et al. The clinical utility of molecular karyotyping using high-resolution array-comparative genomic hybridization. Expert Rev Mol Diagn. Jun 2012; 12(5): 449-57. PMID 22702362
52. Bremer A, Giacobini M, Eriksson M, et al. Copy number variation characteristics in subpopulations of patients with autism spectrum disorders. Am J Med Genet B Neuropsychiatr Genet. Mar 2011; 156(2): 115-24. PMID 21302340
53. Coulter ME, Miller DT, Harris DJ, et al. Chromosomal microarray testing influences medical management. Genet Med. Sep 2011; 13(9): 770-6. PMID 21716121
54. Wincent J, Anderlid BM, Lagerberg M, et al. High-resolution molecular karyotyping in patients with developmental delay and/or multiple congenital anomalies in a clinical setting. Clin Genet. Feb 2011; 79(2): 147-57. PMID 20486943
55. Manolakos E, Vetro A, Kefalas K, et al. The use of array-CGH in a cohort of Greek children with developmental delay. Mol Cytogenet. Nov 09 2010; 3: 22. PMID 21062444
56. Rosenfeld JA, Ballif BC, Torchia BS, et al. Copy number variations associated with autism spectrum disorders contribute to a spectrum of neurodevelopmental disorders. Genet Med. Nov 2010; 12(11): 694-702. PMID 20808228
57. Schaefer GB, Starr L, Pickering D, et al. Array comparative genomic hybridization findings in a cohort referred for an autism evaluation. J Child Neurol. Dec 2010; 25(12): 1498-503. PMID 20729506
58. Shen Y, Dies KA, Holm IA, et al. Clinical genetic testing for patients with autism spectrum disorders. Pediatrics. Apr 2010; 125(4): e727-35. PMID 20231187
59. Bruno DL, Ganesamoorthy D, Schoumans J, et al. Detection of cryptic pathogenic copy number variations and constitutional loss of heterozygosity using high resolution SNP microarray analysis in 117 patients referred for cytogenetic analysis and impact on clinical practice. J Med Genet. Feb 2009; 46(2): 123-31. PMID 19015223
60. Friedman J, Adam S, Arbour L, et al. Detection of pathogenic copy number variants in children with idiopathic intellectual disability using 500 K SNP array genomic hybridization. BMC Genomics. Nov 16 2009; 10: 526. PMID 19917086
61. Baldwin EL, Lee JY, Blake DM, et al. Enhanced detection of clinically relevant genomic imbalances using a targeted plus whole genome oligonucleotide microarray. Genet Med. Jun 2008; 10(6): 415-29. PMID 18496225

62. Christian SL, Brune CW, Sudi J, et al. Novel submicroscopic chromosomal abnormalities detected in autism spectrum disorder. Biol Psychiatry. Jun 15 2008; 63(12): 1111-7. PMID 18374305
63. Marshall CR, Noor A, Vincent JB, et al. Structural variation of chromosomes in autism spectrum disorder. Am J Hum Genet. Feb 2008; 82(2): 477-88. PMID 18252227
64. Pickering DL, Eudy JD, Olney AH, et al. Array-based comparative genomic hybridization analysis of 1176 consecutive clinical genetics investigations. Genet Med. Apr 2008; 10(4): 262-6. PMID 18414209
65. Saam J, Gudgeon J, Aston E, et al. How physicians use array comparative genomic hybridization results to guide patient management in children with developmental delay. Genet Med. Mar 2008; 10(3): 181-6. PMID 18344707
66. Shevell MI, Bejjani BA, Srour M, et al. Array comparative genomic hybridization in global developmental delay. Am J Med Genet B Neuropsychiatr Genet. Oct 05 2008; 147B(7): 1101-8. PMID 18361433
67. Aradhya S, Manning MA, Splendore A, et al. Whole-genome array-CGH identifies novel contiguous gene deletions and duplications associated with developmental delay, mental retardation, and dysmorphic features. Am J Med Genet A. Jul 01 2007; 143A(13): 1431-41. PMID 17568414
68. Ballif BC, Sulpizio SG, Lloyd RM, et al. The clinical utility of enhanced subtelomeric coverage in array CGH. Am J Med Genet A. Aug 15 2007; 143A(16): 1850-7. PMID 17632771
69. Froyen G, Van Esch H, Bauters M, et al. Detection of genomic copy number changes in patients with idiopathic mental retardation by high-resolution X-array-CGH: important role for increased gene dosage of XLMR genes. Hum Mutat. Oct 2007; 28(10): 1034-42. PMID 17546640
70. Hoyer J, Dreweke A, Becker C, et al. Molecular karyotyping in patients with mental retardation using 100K single-nucleotide polymorphism arrays. J Med Genet. Oct 2007; 44(10): 629-36. PMID 17601928
71. Lu X, Shaw CA, Patel A, et al. Clinical implementation of chromosomal microarray analysis: summary of 2513 postnatal cases. PLoS One. Mar 28 2007; 2(3): e327. PMID 17389918
72. Madrigal I, Rodriguez-Revenga L, Armengol L, et al. X-chromosome tiling path array detection of copy number variants in patients with chromosome X-linked mental retardation. BMC Genomics. Nov 29 2007; 8: 443. PMID 18047645
73. Sebat J, Lakshmi B, Malhotra D, et al. Strong association of de novo copy number mutations with autism. Science. Apr 20 2007; 316(5823): 445-9. PMID 17363630
74. Shen Y, Irons M, Miller DT, et al. Development of a focused oligonucleotide-array comparative genomic hybridization chip for clinical diagnosis of genomic imbalance. Clin Chem. Dec 2007; 53(12): 2051-9. PMID 17901113
75. Thuresson AC, Bondeson ML, Edeby C, et al. Whole-genome array-CGH for detection of submicroscopic chromosomal imbalances in children with mental retardation. Cytogenet Genome Res. 2007; 118(1): 1-7. PMID 17901693
76. Wagenstaller J, Spranger S, Lorenz-Depiereux B, et al. Copy-number variations measured by single-nucleotide-polymorphism oligonucleotide arrays in patients with mental retardation. Am J Hum Genet. Oct 2007; 81(4): 768-79. PMID 17847001
77. Ballif BC, Rorem EA, Sundin K, et al. Detection of low-level mosaicism by array CGH in routine diagnostic specimens. Am J Med Genet A. Dec 15 2006; 140(24): 2757-67. PMID 17103431
78. Friedman JM, Baross A, Delaney AD, et al. Oligonucleotide microarray analysis of genomic imbalance in children with mental retardation. Am J Hum Genet. Sep 2006; 79(3): 500-13. PMID 16909388

79. Jacquemont ML, Sanlaville D, Redon R, et al. Array-based comparative genomic hybridisation identifies high frequency of cryptic chromosomal rearrangements in patients with syndromic autism spectrum disorders. J Med Genet. Nov 2006; 43(11): 843-9. PMID 16840569
80. Lugtenberg D, de Brouwer AP, Kleefstra T, et al. Chromosomal copy number changes in patients with non-syndromic X linked mental retardation detected by array CGH. J Med Genet. Apr 2006; 43(4): 362-70. PMID 16169931
81. Menten B, Maas N, Thienpont B, et al. Emerging patterns of cryptic chromosomal imbalance in patients with idiopathic mental retardation and multiple congenital anomalies: a new series of 140 patients and review of published reports. J Med Genet. Aug 2006; 43(8): 625-33. PMID 16490798
82. Miyake N, Shimokawa O, Harada N, et al. BAC array CGH reveals genomic aberrations in idiopathic mental retardation. Am J Med Genet A. Feb 01 2006; 140(3): 205-11. PMID 16419101
83. Rosenberg C, Knijnenburg J, Bakker E, et al. Array-CGH detection of micro rearrangements in mentally retarded individuals: clinical significance of imbalances present both in affected children and normal parents. J Med Genet. Feb 2006; 43(2): 180-6. PMID 15980116
84. Shaffer LG, Kashork CD, Saleki R, et al. Targeted genomic microarray analysis for identification of chromosome abnormalities in 1500 consecutive clinical cases. J Pediatr. Jul 2006; 149(1): 98-102. PMID 16860135
85. Sharp AJ, Hansen S, Selzer RR, et al. Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. Nat Genet. Sep 2006; 38(9): 1038-42. PMID 16906162
86. de Vries BB, Pfundt R, Leisink M, et al. Diagnostic genome profiling in mental retardation. Am J Hum Genet. Oct 2005; 77(4): 606-16. PMID 16175506
87. Schoumans J, Ruivenkamp C, Holmberg E, et al. Detection of chromosomal imbalances in children with idiopathic mental retardation by array based comparative genomic hybridisation (array-CGH). J Med Genet. Sep 2005; 42(9): 699-705. PMID 16141005
88. Tyson C, Harvard C, Locker R, et al. Submicroscopic deletions and duplications in individuals with intellectual disability detected by array-CGH. Am J Med Genet A. Dec 15 2005; 139(3): 173-85. PMID 16283669
89. Harada N, Hatchwell E, Okamoto N, et al. Subtelomere specific microarray based comparative genomic hybridisation: a rapid detection system for cryptic rearrangements in idiopathic mental retardation. J Med Genet. Feb 2004; 41(2): 130-6. PMID 14757861
90. Shaw-Smith C, Redon R, Rickman L, et al. Microarray based comparative genomic hybridisation (array-CGH) detects submicroscopic chromosomal deletions and duplications in patients with learning disability/mental retardation and dysmorphic features. J Med Genet. Apr 2004; 41(4): 241-8. PMID 15060094
91. Vissers LE, de Vries BB, Osoegawa K, et al. Array-based comparative genomic hybridization for the genomewide detection of submicroscopic chromosomal abnormalities. Am J Hum Genet. Dec 2003; 73(6): 1261-70. PMID 14628292
92. Chaves TF, Baretto N, Oliveira LF, et al. Copy Number Variations in a Cohort of 420 Individuals with Neurodevelopmental Disorders From the South of Brazil. Sci Rep. Nov 28 2019; 9(1): 17776. PMID 31780800
93. Hu T, Zhang Z, Wang J, et al. Chromosomal Aberrations in Pediatric Patients with Developmental Delay/Intellectual Disability: A Single-Center Clinical Investigation. Biomed Res Int. 2019; 2019: 9352581. PMID 31781653
94. Xu M, Ji Y, Zhang T, et al. Clinical Application of Chromosome Microarray Analysis in Han Chinese Children with Neurodevelopmental Disorders. Neurosci Bull. Dec 2018; 34(6): 981-991. PMID 29948840

95. Sansovic I, Ivankov AM, Bobinec A, et al. Chromosomal microarray in clinical diagnosis: a study of 337 patients with congenital anomalies and developmental delays or intellectual disability. Croat Med J. Jun 14 2017; 58(3): 231-238. PMID 28613040
96. Ho KS, Twede H, Vanzo R, et al. Clinical Performance of an Ultrahigh Resolution Chromosomal Microarray Optimized for Neurodevelopmental Disorders. Biomed Res Int. 2016; 2016: 3284534. PMID 27975050
97. Ho KS, Wassman ER, Baxter AL, et al. Chromosomal Microarray Analysis of Consecutive Individuals with Autism Spectrum Disorders Using an Ultra-High Resolution Chromosomal Microarray Optimized for Neurodevelopmental Disorders. Int J Mol Sci. Dec 09 2016; 17(12). PMID 27941670
98. Hu G, Fan Y, Wang L, et al. Copy number variations in 119 Chinese children with idiopathic short stature identified by the custom genome-wide microarray. Mol Cytogenet. 2016; 9: 16. PMID 26884814
99. Lu XY, Phung MT, Shaw CA, et al. Genomic imbalances in neonates with birth defects: high detection rates by using chromosomal microarray analysis. Pediatrics. Dec 2008; 122(6): 1310-8. PMID 19047251
100. Gogarty B. Parents as partners. A report and guidelines on the investigation of children with developmental delay; by parents, for professionals Cambridge: Cambridge Genetics Knowledge Park; 2006.
101. Mroch AR, Flanagan JD, Stein QP. Solving the puzzle: case examples of array comparative genomic hybridization as a tool to end the diagnostic odyssey. Curr Probl Pediatr Adolesc Health Care. Mar 2012; 42(3): 74-8. PMID 22325475
102. Turner G, Boyle J, Partington MW, et al. Restoring reproductive confidence in families with X-linked mental retardation by finding the causal mutation. Clin Genet. Feb 2008; 73(2): 188-90. PMID 18070138
103. Lingen M, Albers L, Borchers M, et al. Obtaining a genetic diagnosis in a child with disability: impact on parental quality of life. Clin Genet. Feb 2016; 89(2): 258-66. PMID 26084449
104. Hayeems RZ, Hoang N, Chenier S, et al. Capturing the clinical utility of genomic testing: medical recommendations following pediatric microarray. Eur J Hum Genet. Sep 2015; 23(9): 1135-41. PMID 25491637
105. Ellison JW, Ravnan JB, Rosenfeld JA, et al. Clinical utility of chromosomal microarray analysis. Pediatrics. Nov 2012; 130(5): e1085-95. PMID 23071206
106. Hoffmann TJ, Windham GC, Anderson M, et al. Evidence of reproductive stoppage in families with autism spectrum disorder: a large, population-based cohort study. JAMA Psychiatry. Aug 2014; 71(8): 943-51. PMID 24942798
107. Grozeva D, Carss K, Spasic-Boskovic O, et al. Targeted Next-Generation Sequencing Analysis of 1,000 Individuals with Intellectual Disability. Hum Mutat. Dec 2015; 36(12): 1197-204. PMID 26350204
108. Kalsner L, Twachtman-Bassett J, Tokarski K, et al. Genetic testing including targeted gene panel in a diverse clinical population of children with autism spectrum disorder: Findings and implications. Mol Genet Genomic Med. Mar 2018; 6(2): 171-185. PMID 29271092
109. Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. Feb 2014; 53(2): 237-57. PMID 24472258
110. Michelson DJ, Shevell MI, Sherr EH, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. Oct 25 2011; 77(17): 1629-35. PMID 21956720

111. Manning M, Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med. Nov 2010; 12(11): 742-5. PMID 20962661
112. Manning M, Hudgins L. Addendum: Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med. Jun 08 2020. PMID 32514088
113. South ST, Lee C, Lamb AN, et al. ACMG Standards and Guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: revision 2013. Genet Med. Nov 2013; 15(11): 901-9. PMID 24071793
114. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med. May 2013; 15(5): 399-407. PMID 23519317
115. Lipkin PH, Macias MM, Norwood KW, et al. Promoting Optimal Development: Identifying Infants and Young Children With Developmental Disorders Through Developmental Surveillance and Screening. Pediatrics. Jan 2020; 145(1). PMID 31843861

*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through June 24, 2024, the date the research was completed.*

## Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|---|---|---|---|
| 3/1/09 | 1/29/09 | 12/9/08 | Joint policy established |
| 9/1/12 | 6/12/12 | 6/19/12 | Routine maintenance. Policy reformatted to mirror BCBSA policy. No change to position statement or inclusions/ exclusions. Codes added to policy, which will be effective in 2013. |
| 7/1/13 | 4/16/13 | 4/22/13 | Routine update. 81228 and 81229 codes changed to established. References added. |
| 9/1/14 | 6/17/14 | 6/23/14 | Updated CPT code nomenclature, updated references, added “Genetic Testing for FMR1 mutations (including Fragile X Syndrome)” as a related policy. Added exclusion and supporting rationale to policy regarding genetic testing of products of conception following miscarriage or idiopathic recurrent pregnancy loss (RPL). |
| 11/1/15 | 8/18/15 | 9/14/15 | Updated rationale and references; removed all information related to prenatal CMA testing.<br><br>Policy statements changed to indicated that CMA 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.<br><br>Updated title to mirror BCBSA title. |
| 11/1/16 | 8/16/16 | 8/16/16 | Routine policy maintenance, no change in policy status. |

| | | | |
|---|---|---|---|
| 11/1/17 | 8/15/17 | 8/15/17 | Updated rationale, added references 5, 7, 24, 26, 27, 30, 32-34, 38 and 40. No change in policy status. |
| 11/1/18 | 8/21/18 | 8/21/18 | Routine policy maintenance. No changes in policy status. |
| 11/1/19 | 8/20/19 | | Removed Medicaid section. No changes in policy status. |
| 11/1/20 | 8/18/20 | | Rationale reorganized, tables for studies added. No change in policy status. |
| 11/1/21 | 8/17/21 | | Routine maintenance. No references added. No change in policy status. |
| 11/1/22 | 8/16/22 | | Routine maintenance |
| 11/1/23 | 8/15/23 | | Routine maintenance.<br>No change in policy status.<br>Codes 0156U, 0170U, 0209U, and 0318U added to policy as E/I.<br>Vendor: N/A. (ky) |
| 11/1/24 | 8/20/24 | | Routine maintenance.<br>Vendor: Avalon M2176 - Testing for Autism Spectrum Disorder and Developmental Delay: 12/6/23.<br>Codes 81470, 81471, and 0170U are on this Avalon policy as not meeting coverage criteria. JUMP policy has these codes as E/I. (ky) |

Next Review Date: 3rd Qtr. 2025

# BLUE CARE NETWORK BENEFIT COVERAGE
# POLICY: GENETIC TESTING - CHROMOSOMAL MICROARRAY ANALYSIS AND NEXT-GENERATION SEQUENCING PANELS, FOR THE EVALUATION OF CHILDREN WITH DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER, AND/OR CONGENITAL ANOMALIES

## I. Coverage Determination:

| | |
|---|---|
| **Commercial HMO (includes Self-Funded groups unless otherwise specified)** | Covered; criteria apply. |
| **BCNA (Medicare Advantage)** | See government section. |
| **BCN65 (Medicare Complementary)** | Coinsurance covered if primary Medicare covers the service. |

## II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.