2.04.59	Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies		
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Section:	2.0 Medicine	**Page:**	Page 1 of 32

Policy Statement

I. Chromosomal microarray analysis (CMA) or low-pass genome sequencing for the detection of copy number variants (e.g., CNGnome) may be considered **medically necessary** as first-line testing in the initial evaluation (see Policy Guidelines) of individuals with **any** of the following:
   A. Apparent nonsyndromic developmental delay/intellectual disability
   B. Autism spectrum disorder
   C. Multiple congenital anomalies not specific to a well-delineated genetic syndrome

II. Chromosomal microarray (CMA) or low-pass genome sequencing for the detection of copy number variants (e.g., CNGnome) is considered **investigational** for the evaluation of all other conditions of delayed development, including, but not limited to, idiopathic growth or language delay.

III. 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.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Use of chromosomal microarray (CMA) testing as outlined in this policy is not intended for use in the prenatal period.

A guideline update from the American College of Medical Genetics (Schaefer et al [2013]) stated 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 CMA testing.

Recommendations from the American College of Medical Genetics (Manning and Hudgins [2010]) on array-based technologies and their clinical utilization for detecting chromosomal abnormalities include the following: “Appropriate follow-up is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH [fluorescent in situ hybridization] studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.”

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

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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.

Coding

The following codes (81228 and 81229) cannot be reported together.

- **81228**: Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
- **81229**: Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis

There are specific CPT codes for genomic sequencing panels for X-linked intellectual disability that meet the criteria in the code descriptor:

- **81470**: X-linked intellectual disability (XLID) (e.g., 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
- **81471**: X-linked intellectual disability (XLID) (e.g., 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

If testing is performed that does not meet the above code descriptors, it would be reported with the unlisted molecular pathology code 81479.

The following is a CPT Proprietary Laboratory Analyses (PLA) code that represents the SMASH (Short Multiply Aggregated Sequence Homologies) test by Marvel Genomics

- **0156U**: Copy number (e.g., intellectual disability, dysmorphology), sequence analysis

The following is a CPT PLA code that represents the Clarifi™ autism saliva test designed to provide a probability of autism diagnosis based on biomarkers in saliva for the use in children 18 months to 6 years of age:

- **0170U**: Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis

The following is a PLA code for CNGnome that detects intellectual disability or global developmental delay, multiple congenital anomalies, ASD, suspected chromosomal imbalances including micro-deletion syndromes, uniparental isodisomy, and autosomal recessive conditions due to consanguinity. The DNA specimen is extracted from blood or saliva. The test uses next generation sequencing.

- **0209U**: Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities

The following PLA code was created to allow a generic cytogenomics code for specific reporting of low pass sequencing methods for chromosomal analysis procedures.

- **81349:** Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis

Description

Chromosomal microarray (CMA) testing has been proposed for the detection of genetic imbalances in infants or children with characteristics of developmental delay/intellectual disability, autism spectrum disorder, and/or congenital anomalies. CMA testing increases the diagnostic yield over karyotyping in children with the aforementioned characteristics, and CMA testing may impact clinical management decisions. Next-generation sequencing panel testing allows for the simultaneous analysis of a large number of genes and, in patients with normal CMA testing, next-generation testing has been proposed as a way to identify single-gene causes of syndromes that have autism as a significant clinical feature.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Lab tests for CMA testing and next-generation sequencing are available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 2010, the FDA indicated that it would require microarray manufacturers to seek clearance to sell their products for use in clinical cytogenetics.

CMA Testing

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

In January 2014, the Affymetrix CytoScan® Dx Assay (Thermo Fisher Scientific) was cleared by the FDA through the de novo 510(k) process. The FDA's review of the CytoScan Dx Assay included an analytic evaluation of the test's ability to detect accurately numerous chromosomal variations of different types, sizes, and genome locations compared with several analytically validated test methods. The FDA found that the CytoScan Dx Assay could detect CNVs across the genome and adequately detect CNVs in regions of the genome associated with developmental delay/intellectual disability. Reproducibility decreased with the CNV gain or loss size, particularly when less than approximately 400 kilobases (generally recommended as the lower reporting limit). As of July 2017, Affymetrix™ contains 2.7 million markers for copy number, 750,000 SNVs, and 1.9 million non-polymorphic probes (Affymetrix was acquired by Thermo Fisher Scientific in 2016). 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 88435 custom probes designed by Lineagen.

Ambry Genetics offers multiple tests (CMA and next-generation sequencing) 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 next-generation sequencing panel for neurodevelopmental disorders assesses 196 genes.

LabCorp offers the Reveal® SNP Microarray-Pediatric for individuals with nonsyndromic congenital anomalies, dysmorphic features, developmental delay/intellectual disability, 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 next-generation sequencing panels designed for the evaluation of ASD, developmental delay/intellectual disability, and congenital anomalies, which vary in terms of the numbers of and specific genes tested.

Emory Genetics Laboratory offers a next-generation sequencing ASD panel of genes targeting genetic syndromes that include autism or autistic features. Greenwood Genetics Center offers a next-generation sequencing panel for syndromic autism that includes 83 genes. Fulgent Genetics offers a next-generation sequencing ASD panel that includes hundreds of genes.

Rationale

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 developmental delay /intellectual disability and autism spectrum disorder (ASD) but more often reflect the 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, the cytogenetic analysis will discover chromosomal abnormalities that require study to determine their significance.

Prior to the advent of chromosomal microarray (CMAs), the initial step in the cytogenetic analysis was G-banded karyotyping, which evaluates all chromosomes. High-resolution G-banding can detect changes as small as 3 to 5 megabases in size, although standard G-banding evaluates more than 10 megabases changes. In children with developmental delay/intellectual disability, a review by Stankiewicz and Beaudet (2007) found G-banded karyotyping diagnostic in approximately 3% to 5% of cases.[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 developmental delay and intellectual disability,[5,]and was 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 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,] offers 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 fluorescent dyes. Comparative fluorescence intensity will be increased when there are duplications and diminished with deletions. The resolution provided by aCGH is higher than with SNV arrays. In addition, aCGH has better signal-to-background characteristics than SNV arrays. In contrast to aCGH, SNV arrays will also identify long stretches of DNA homozygosity, which may suggest uniparental disomy or consanguinity. Uniparental disomy occurs when a child inherits 2 copies of a chromosome from 1 parent and no copies from the other parent. Uniparental disomy can lead to syndromes such as Angelman and Prader-Willi.

Table 1 summarizes the cytogenetic tests used to evaluate children with developmental delay/intellectual disability 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] 1 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 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 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. Next-generation sequencing involves the sequencing of millions of fragments of genetic material in a massively parallel fashion. Next-generation sequencing can be performed on segments of the genetic material of various sizes from the entire genome (whole-genome sequencing) to small subsets of genes (targeted sequencing). Next-generation sequencing allows the detection of SNVs, CNVs, insertions, and deletions. With higher resolution comes a 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 and 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, 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 the 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 an association between CNV and phenotype, and findings in "normal" individuals.

The American College of Medical Genetics 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 the interpretation of clinically significant copy number variation."[12,] The proposal defined levels of evidence that describe how well or how poorly detected variants or CNVs correlate with phenotype.

Literature Review

This review has been informed by a Technology Evaluation Center (TEC) Assessment 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, intellectual disability, 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Developmental Delay/Intellectual Disability

Developmental delay is diagnosed in children 5 years or younger who show a significant delay in 2 or more developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living.[15,] Developmental delay can precede the development of intellectual disability as the child ages.[16,]

Intellectual disability 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 intellectual disability 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 intellectual disability; most genes (>90%) are associated with syndromes.[19,] Inheritance of intellectual disability 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 intellectual disability 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 developmental delay and intellectual disability. 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 developmental delay/intellectual disability 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 defines ASD[15,] 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 2 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 4 to 5 times more common in boys than girls, and white children are more often identified with ASD than black or Hispanic children. An accurate diagnosis can generally be made by age 2. 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,]

Chromosomal Microarray Testing

Clinical Context and Test Purpose

The purpose of CMA testing is to identify a genetic cause for individuals with developmental delay/intellectual disability, 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 is children with developmental delay/intellectual disability, ASD, and congenital anomalies for whom the cause of the disorder has not been identified despite other established methods such as karyotyping.

Interventions

The relevant 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 developmental delay/intellectual disability, ASD, and congenital anomalies: karyotyping. 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 of developmental delay/intellectual disability 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, or

- 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, which are summarized in Table 3. The median diagnostic yield in developmental delay/intellectual disability 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 Developmental Delay, Intellectual Disability, and ASD Published Before 2015

Study	N	Diagnoses	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 an abnormality on karyotype but it did not convey a definite cause of patients' disorder	25
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
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
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 a 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

Study	N	Diagnoses	Patient Description	Previous Normal Studies	Yield, %
Preiksaitiene et al (2014)[37,]	211	DD/ID	Syndromic and nonsyndromic cases of unknown 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 a clinical geneticist	Not specified	11.3
Utine et al (2014)[42,]	100	ID	Idiopathic ID	Karyotype, FISH	12
Uwineza et al (2014)[43,]	50	DD/ID	DD/ID/MCA	Karyotype	26
Battaglia et al (2013)[44,]	349	DD/ID/ASD	Idiopathic DD/ID/ASD or dysmorphia	FISH or karyotype	22.1
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
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	25.2
Iourov et al (2012)[49,]	54	ID/ASD/CA	Highly selected patients from a group of 2426 patients based on clinical and cytogenic data	G-banded karyotype	28
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	Karyotype	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

Study	N	Diagnoses	Patient Description	Previous Normal Studies	Yield, %
Shen et al (2010)[58],	848	ASD	Idiopathic MR and/or dysmorphism or MCAs	G-banded karyotype, fragile X	7
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
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
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
Aradhya et al (2007b)[67],	20	DD/ID	As above	As above	50
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
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

Study	N	Diagnoses	Patient Description	Previous Normal Studies	Yield, %
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
Jacquemont et al (2006)[79,]	29	ASD	Syndromic ASD	Karyotype, biochemical tests	28
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
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
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
Vissers et al (2003)[91,]	20	DD/ID	Idiopathic MR and dysmorphism; patients scored >3 on de Vries Checklist (2001)	Karyotype	10

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

Six additional studies published after 2015 are summarized in Table 4.[92,93,94,95,96,97,] The diagnostic yields were generally higher than in studies conducted prior to 2016. 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] The overlap of patients in the 2 reports is unclear.

Table 4. Diagnostic Yield of Studies of Patients With Developmental Delay, Intellectual Disability, 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) • 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) • 33 (excluding ASD) • 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) • 33 (excluding ASD) • 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 the 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

Study	N	Diagnoses	Patient Description	Previous Normal Studies	Yield
					would not have been defined by karyotyping

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

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.

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 developmental delay/intellectual disability, 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 the establishment of a definitive diagnosis in patients with developmental delay/intellectual disability, ASD, and/or congenital anomalies leads to changes in management that are likely to improve outcomes. Of particular interest is the use of CMA testing to make a specific genetic diagnosis in a patient with developmental delay/intellectual disability, 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 6 retrospective studies that examined the potential impact of CMA results on clinical decisions are summarized in Table 6. 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] 72 (9.6)[g]	114	• 79.6% (364/457) with reportable results • 62.4% (184/295) with benign results received medical recommendations	• Specialist consults: 221 (37.7) • Imaging: 125 (21.3) • Lab tests: 70 (12.0) • Surveillance: 88 (15.0) • 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) • Screening: 11 (5.9) • Imaging: 38 (20.3) • 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] 5.8[b]	121[a,c] 73[a,c]	65 (53.7)[a] 25 (34.2)[b]	• Referral: 67 (60)[a] and 11 (29)[b] • Imaging: 25 (22)[a] and 9 (24)[b] • 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) • Screening: 8 (16.7) • Avoid further genetic testing: 12 (25)

Study	Dates Testing	Patients (Tests)	Diagnostic Yield, n (%) or %	Pathogenic, n	Actionable, n (%)	Clinical Management Changes, n (%)
						• 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 [CI], 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 (i.e., 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% 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 (i.e., not found in parents)

ASD: autism spectrum disorder; ID: intellectual disability.

Section Summary: Chromosomal Microarray Testing

The evidence for use of CMA testing for a definitive diagnosis in individuals with developmental delay/intellectual disability, ASD, and/or congenital anomalies consists of studies reporting on the yield of a positive test in affected individuals, combined with a chain of evidence to support the clinical utility of testing. The testing yield varies by 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 is to identify a genetic cause for individuals with developmental delay/intellectual disability, 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 is children with developmental delay/intellectual disability, ASD, and congenital anomalies for whom the cause of the disorder has not been identified after CMA testing.

Interventions

The relevant intervention of interest is gene panel testing with next-generation sequencing. 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. 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 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 met the following eligibility criteria were considered:

- case series or cohort studies that enrolled 20 or more patients with clinical diagnoses of developmental delay/intellectual disability or ASD with known or suspicion of genetic abnormalities, with or without negative results by CMA testing on enrolled patients, or
- 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 a next-generation sequencing panel.[108,]

Table 8. Diagnostic Yield Studies Published

Study	N	Diagnoses	Patient Description	Previous Normal Studies	Yield
Kalsner et al (2018) [108,]	100	ASD	Consecutive children referred to a single U.S. neurogenetics clinic with a 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 CHD; 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% had likely pathogenic rare variant (8% had likely pathogenic loss-of-function variant and 3% had 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 Panel Testing

It is arguable that a chain of evidence for the use of CMA testing in evaluating developmental delay/intellectual disability, ASD, and/or congenital anomalies would apply to next-generation sequencing panels. However, the clinical validity of next-generation sequencing panels is less well-established than for CMA. The testing yield and likelihood of an uncertain result are variable, based on the gene panel, gene tested, and patient population. There are real risks of uninterpretable and incidental results. Therefore, current evidence does not permit conclusions on whether next-generation sequencing panel testing improves outcomes.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

In 2014, the American Academy of Pediatrics (AAP) issued a clinical report on the optimal medical genetics evaluation of a child with developmental delays or intellectual disability.[15,] Regarding chromosomal microarray (CMA) testing, this report stated: “CMA now should be considered a first-tier diagnostic test in all children with [global developmental delay/intellectual disability] 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.[109,] 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).[110,] 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 Child Neurology Society updated their guidelines on the evaluation of unexplained developmental delay and intellectual disability with information on genetic and metabolic (biochemical) testing to accommodate advances in the field.[111,] The guidelines concluded that CMA testing has the highest diagnostic yield in children with developmental delay/intellectual disability, 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 acknowledged 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 a clinical practice resource on array-based technologies and their clinical utilization for detecting chromosomal abnormalities.[112,113,] CMA testing for copy number variants was 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 nonsyndromic developmental delay/intellectual disability
- Autism spectrum disorder (ASD)

Other ACMG guidelines have addressed the design and performance expectations for clinical microarrays and associated software[8,114,] and for the interpretation and reporting of copy number variants,[11,] both intended for the postnatal setting.

A 2013 update included recommendations on the validation of microarray methodologies for both prenatal and postnatal specimens.[115,]The guideline revisions from ACMG (2013) stated that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of ASD is recommended, with the first tier including fragile X syndrome and CMA, and the second tier *MECP2* and *PTEN* testing.[116,] The guidelines stated 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.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in August 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

Please provide the following documentation:

- Current history and physical and/or consultation notes including:
  - Birth records (if applicable)
  - Diagnosis
  - Genetic counseling notes (if applicable)
  - Treatment plan (if applicable)
- Specific test(s) requested
- Name of the test being requested or the Concert Genetics GTU identifier The Concert Genetics GTU can be found at https://app.concertgenetics.com

Post Service (in addition to the above, please include the following):

- Laboratory report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0156U	Copy number (e.g., intellectual disability, dysmorphology), sequence analysis
	0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis

Type	Code	Description
	0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
	81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
	81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
	81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
	81470	X-linked intellectual disability (XLID) (e.g., 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
	81471	X-linked intellectual disability (XLID) (e.g., 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
HCPCS	S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/06/2012	BCBSA Medical Policy adoption
07/31/2015	Coding update
10/30/2015	Policy title change from Chromosomal Microarray Analysis (CMA) for the Genetic Evaluation of Patients with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder Policy revision with position change
11/01/2016	Policy title change from 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 Policy revision without position change
08/01/2017	Coding update
10/01/2017	Policy revision without position change
10/01/2018	Policy revision without position change
12/01/2018	Policy revision without position change
12/01/2018	Policy revision without position change
12/01/2019	Policy revision without position change

Effective Date	Action
03/01/2020	Coding update
07/01/2020	Coding update
12/01/2020	Annual review. Policy statement, guidelines and literature updated. Coding update.
12/01/2021	Annual review. Policy guidelines and literature updated.
03/01/2022	Coding update
11/01/2022	Coding update
12/01/2022	Annual review. No change to policy statement. Literature review updated
12/01/2023	Annual review. Policy statement, guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	AFTER
Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies 2.04.59 **Policy Statement:** I. Chromosomal microarray analysis (CMA) or low-pass genome sequencing for the detection of copy number variants (e.g., CNGnome) may be considered **medically necessary** as first-line testing in the initial evaluation (see Policy Guidelines) of individuals with **any** of the following: A. Apparent nonsyndromic developmental delay/intellectual disability B. Autism spectrum disorder C. Multiple congenital anomalies not specific to a well-delineated genetic syndrome II. Chromosomal microarray (CMA) or low-pass genome sequencing for the detection of copy number variants (e.g., CNGnome) is considered **investigational** for the evaluation of all other conditions of delayed development, including but not limited to idiopathic growth or language delay. III. 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. Standard whole exome testing after negative CMA testing is addressed in a separate policy: 2.04.102 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders	**Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies 2.04.59** **Policy Statement:** I. Chromosomal microarray analysis (CMA) or low-pass genome sequencing for the detection of copy number variants (e.g., CNGnome) may be considered **medically necessary** as first-line testing in the initial evaluation (see Policy Guidelines) of individuals with **any** of the following: A. Apparent nonsyndromic developmental delay/intellectual disability B. Autism spectrum disorder C. Multiple congenital anomalies not specific to a well-delineated genetic syndrome II. Chromosomal microarray (CMA) or low-pass genome sequencing for the detection of copy number variants (e.g., CNGnome) is considered **investigational** for the evaluation of all other conditions of delayed development, including, but not limited to, idiopathic growth or language delay. III. 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.