Chromosomal Microarray Analysis (CMA) or Copy Number Analysis for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies

Effective: August 1, 2023

Next Review: April 2024
Last Review: June 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Chromosomal microarray (CMA) and copy number testing have been proposed for detection of genetic imbalances in patients with characteristics of developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), and/or congenital anomalies. This testing, including array comparative genomic hybridization (aCGH) and single nucleotide variant (SNV) arrays, increases the diagnostic yield over karyotyping in this population and may impact clinical management decisions.

MEDICAL POLICY CRITERIA

Note: This policy does not address fetal testing, single gene testing, panel testing, whole exome or whole genome sequencing. Please refer to the Cross References section below. For a list of investigational panel tests, see Genetic Testing Policy No. 64, *Evaluating the Utility of Genetic Panels*.

I. Chromosomal microarray analysis or copy number analysis may be considered **medically necessary** in patients with any of the following conditions:

A. Apparent nonsyndromic cognitive developmental delay/intellectual disability (DD/ID); or

B. Autism spectrum disorder (ASD); or

C. Multiple congenital anomalies not specific to a well-delineated genetic syndrome. Congenital anomaly is defined as an anomaly that is present at birth.

II. Postnatal chromosomal microarray analysis or copy number analysis for developmental delay, intellectual disability, autism spectrum disorder, or congenital anomalies is considered **investigational** when Criteria I. above is not met, including for asymptomatic adults.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing, including any intellectual/cognitive disability, autism spectrum disorder, and any congenital anomalies.
   - Date of sample collection (blood draw)
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Preimplantation Genetic Testing of Embryos, Genetic Testing, Policy No. 18
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Genetic Testing for FMR1 and AFF2 Variants (including Fragile X and Fragile XE Syndromes), Genetic Testing, Policy No. 43
4. Genetic Testing for Diagnosis and Management of Behavioral Health Conditions, Genetic Testing, Policy No. 53
5. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
6. Whole Exome and Whole Genome Sequencing, Genetic Testing, Policy No. 76
7. Invasive Prenatal (Fetal) Diagnostic Testing Using Chromosomal Microarray Analysis (CMA), Genetic Testing, Policy No. 78
8. Genetic Testing for the Evaluation of Products of Conception and Pregnancy Loss, Genetic Testing, Policy No. 79
9. Genetic Testing for Epilepsy, Genetic Testing, Policy No. 80
10. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

Chromosomal microarray (CMA) testing has been proposed for detection of genetic imbalances in patients with characteristics of developmental delay/intellectual disability or autism spectrum disorders. There are two different CMA platforms currently being used in the diagnostic setting to detect microdeletions and microduplications; array comparative genomic hybridization (aCGH) and single nucleotide variant (SNV) arrays, also known as single nucleotide polymorphism (SNP) arrays. CMA increases the diagnostic yield over karyotyping in this population and may impact clinical management decisions.

DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY

Developmental delay (DD) is diagnosed in children aged five years or younger who show significant delay in two or more developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living.[1] DD can precede the development of intellectual disability (ID) as the child ages.[2]

ID is manifest by significant limitations in intellectual functioning and adaptive behavior. It is diagnosed at or after age five (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.[3]

Prevalence estimates of GDD and ID range from 1% to 3%.[4] Both are influenced by genetic, environmental, infectious, and perinatal factors. Approximately 450 genes have been causally related to ID; most genes (approximately 90%) are associated with syndromes.[5] 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.[6] With use of whole genome sequencing, they estimated almost 60% of cases have an identifiable genetic etiology.

Congenital anomalies are frequently present in children with GDD and ID. In addition, a suspected etiology can often be established from history and physical examination (in as much as 20% to 40% of cases) without genetic testing.[7] The recommended approach to evaluation in GDD/ID begins with a three-generation family history and physical (including neurologic) exam. Subsequent testing is used to confirm a suspected diagnosis (e.g., targeted 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 chromosomal microarray (CMA) testing (without karyotyping) are recommended—regardless of the presence or absence of dysmorphologic features or congenital anomalies.[1]

AUTISM SPECTRUM DISORDER

DSM-5 defines autism spectrum disorder (ASD) as the presence of:[3]

- Persistent deficits in social communication and social interaction across multiple contexts,
- Restricted, repetitive patterns of behavior, interests, or activities,
- Symptoms must be present in the early developmental period (typically recognized in

the first two years of life), and
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

In 2010, the estimated prevalence of ASD among eight-year-olds was 14.7 per 1000 or 1 in 68.[8] 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. Evaluation includes developmental screening and diagnostic evaluation (i.e., hearing, vision, neurologic, 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%.[9] A family with an affected child has a 13% to 19% risk for recurrence in subsequent children.[10] Based on Swedish genetic studies, Gaugler (2014) concluded that "the bulk of autism arises from genetic variation" (as opposed to environmental causes).[11] Still, although genetic determinants can be heritable, most appear to arise de novo.[9] For these reasons, a child with ASD is often evaluated with genetic testing.

DIAGNOSTIC TESTING

Karyotyping and Fluorescence 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 ASD but more often reflect normal genetic variation.[12] However, de novo CNVs are observed about four times more frequently in children with ASD than in normal individuals.[9] 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 three to five 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%.[13] In ASD, high-resolution karyotyping appears to identify abnormalities in up to 5% of cases.[14]

In contrast, molecular cytogenetic techniques can detect small submicroscopic chromosomal alterations. Fluorescence 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,[15] diagnostic in approximately 5% to 6% of those with negative karyotypes, but uncommonly in ASD.[16]

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. 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 two 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 two copies of a chromosome from one parent and no copies from the other parent. UPD can lead to syndromes such as Angelman and Prader-Willi.

Microarrays may be prepared by the laboratory using the technology or, more commonly, by commercial manufacturers, and sold to laboratories that must qualify and validate the product for use in their assay, in conjunction with computerized software for interpretation. The proliferation of laboratory-developed and commercially available platforms prompted the American College of Medical Genetics (ACMG) to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting.[17]

GENETIC ASSOCIATIONS WITH DD/ID AND ASD

For common phenotypes and syndromes, the pathogenicity of CNVs may be supported by considerable evidence; for uncommon phenotypes and uncommon CNVs determining pathogenicity requires a systematic evaluation that includes parental studies, examining databases for reported associations, and considering the molecular consequences of the identified variant. Parental studies (e.g., “trio” testing of affected child, father, and mother) can identify an inherited CNV from an unaffected parent and therefore considered benign.[18] 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, 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.[19] 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 ACMG has published guidelines for evaluating, interpreting, and reporting pathogenicity reflecting these principles.[20] 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.”[21] The proposal defined levels of evidence that describe how well or how poorly detected variants or CNVs correlate with phenotype.

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 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 these tests, though some have received marketing clearance.

COMMERCIALLY AVAILABLE TESTS

CMA testing is commercially available through many laboratories and includes targeted and whole- genome arrays, with or without SNV analysis. Some of these tests are described below.

GeneDx’s GenomeDx is a whole genome array intended for postnatal cases. It also contains SNV probes and also targets at the exon level 65 genes associated with neurodevelopmental disorders.

In 2014 the FDA cleared the Affymetrix CytoScan® Dx Assay for marketing through its de novo 501(k) classification process. The FDA’s review of the CytoScan® Dx Assay included an analytical evaluation of the test’s ability to accurately detect numerous chromosomal variations of different types, sizes, and genome locations when compared to 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. As of July 2017, Affymetrix reported 2.69 million markers for copy number, 750,000 biallelic probes, and 1.9 million polymorphic probes. Affymetrix™ was acquired by Thermo Fisher Scientific in 2016.

FirstStep^{Dx} PLUS® 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. FirstStep^{Dx} PLUS® is an integrated service that combines proprietary genetic testing, reporting, and genetic counseling.

Ambry Genetics offers a 180K oligo array and a combined SNV + CGH array and states that the tests should be considered for all individuals with syndromic or non-syndromic conditions that may be caused by genomic imbalance. As of July 2017, the CMA offered by Ambry Genetics includes over 2.6 million probes for copy number and 750,000 SNV probes.

LabCorp offers the Reveal SNP Microarray-Pediatric and states that the test is intended for individuals with non-syndromic congenital anomalies, dysmorphic features, DD, mental retardation, ID and/or ASD. The Reveal microarray has 2,695 million probes as of July 2017.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[22] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. Clinical validity, which refers to the diagnostic performance of the test (i.e., sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. Clinical utility, which refers to how the results of the diagnostic test will be used to change disease management and whether these changes in management lead to clinically important improvements in health outcomes.

The 2015 BCBSA TEC Special Report on CMA for global DD, ID, and ASD reviewed the evidence for the analytic validity of CMA testing, and made the following conclusions: "In summary, acceptable analytic validity is generally assumed for CMA testing based on laboratories meeting quality standards under CLIA, including participation in proficiency testing. Reports of analytic validity specific to CMA are not readily identified. Data supporting the analytic validity of the CytoScan Dx® Assay for use in children with ID and GDD were included as part of the FDA clearance."[23] The following evidence review is focused on clinical validity and utility.

CMA FOR THE DIAGNOSIS OF DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDERS AND CONGENITAL ANOMALIES IN CHILDREN AND ADOLESCENTS

Clinical validity

There is sufficient evidence of the clinical validity of CMA testing for children and adolescents for the evaluation of developmental delay/intellectual disability, autism spectrum disorder and congenital anomalies. This evidence consists of large case series and cohort studies testing between 200 and 15,000 patients with CMA. The diagnosis rates reported in these large studies ranges from 5% to 26%, depending on the study and the indication.[24-35] Although few

studies report VUS rates, the more recent studies report VUS rates within the same range as CNVs determined to be pathogenic (9% to 20%).

Clinical Utility

Neither standard cytogenetic analysis nor CMA analysis have been systematically studied for impact on clinical outcomes other than diagnosis[36, 37]; Schaefer and Mendelsohn[16] acknowledge, for example, that a genetic diagnosis "typically will not change interventions for the [autism] patient." Rather, clinical utility of genetic testing is primarily inferred based on the value of diagnosis to the family, estimation of recurrence risk, and on the importance of early detection and early intervention.[37]

Guidelines emphasize the importance of cytogenetic evaluation to look for certain kinds of variants that may be linked to specific conditions for early diagnosis and intervention. However, the benefits of early intervention for these disorders are uncertain. Few randomized trials have been conducted and the interventions differ considerably, indicating that the field is still early in researching the critical elements of effective early intervention. For well-characterized genetic syndromes, it is important to incorporate monitoring for co-morbidities known to be associated with the condition. For example, 22q11 microdeletion syndrome (includes DiGeorge and velocardiofacial syndromes) is associated with development of hearing impairment in a significant proportion of patients, with subsequent delayed speech.[38] Velocardiofacial syndrome is also associated with heart defects.[3] Klinefelter syndrome may first be detected as developmental delay in early childhood; androgen treatment is an important component of therapy.[3]

A reasonable body of literature has evaluated whether 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.

Several retrospective studies have been published that examined the potential impact of CMA results on clinical decisions, including referral to other specialists and further evaluations for associated symptoms.[39-44] Additional clinical action was taken based on CMA result between 45% to 80% of the time, depending on the study and the indication diagnosed. 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 and noted as an outcome in case series and reports.[45] Saam (2008) noted that CMA testing may influence that odyssey.[43] 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 (2016) has reported a benefit for maternal quality of life if aCGH tests succeed

to clarify the etiologic diagnosis in an affected child.[46]

Section Summary

Chromosomal microarray (CMA) testing has been proposed for detection of genetic imbalances in patients with characteristics of developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), and/or congenital anomalies. Although systematic studies of the impact of CMA on patient outcomes are lacking, the improvement in diagnostic yield over karyotyping has been well-demonstrated, and, 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. Thus, there is sufficient evidence of the analytical validity, clinical validity and clinical utility of CMA testing for children and adolescents for the evaluation of developmental delay/intellectual disability, autism spectrum disorder and congenital anomalies, and the scientific evidence will no longer be reviewed for CMA testing for children and adolescents for the evaluation of these indications.

CMA TESTING IN ADULTS

Clinical Validity

Ho (2016) published a study on the clinical performance of an ultrahigh-resolution chromosomal microarray optimized for neurodevelopmental disorders, including developmental delay (DD), intellectual disability (ID), and autism spectrum disorder (ASD), on a series of 5,487 patients over 3.5 years.[47] A subset of 225 patients was comprised of adults over 18 years old, which were analyzed separately from the pediatric patients. In patients where the indication for testing was either ID (n=119) or multiple congenital anomalies (MCA) (n=35), the rate of pathogenic CNVs in adult patients tested were the highest of any age group, similar at levels similar to the first year of life: (16.8% and 20.0%, resp.). The authors note that this could be due to the relatively small size of this cohort, or alternatively, it may be more reflective of severity in that particular age group. The VUS rate in adults with ID was higher than any other age group analyzed (21.8%), but lower in adults with MCG (14.8%).

Costain (2013) used high-resolution genome-wide microarrays to investigate rare CNVs in a prospectively recruited community-based cohort of 459 unrelated adults with schizophrenia.[48] A blinded review by two independent clinical cytogenetic laboratory directors of all large (>500 kb) rare CNVs in cases and well-matched controls showed that those deemed to be clinically significant were highly enriched in schizophrenia (16.4-fold increase, $p<0.0001$). In this cohort, 23 of the 459 adult patients (5.0%) were found to have a pathogenic rare CNV. The investigators state that their findings suggest consideration of a potential role for clinical microarray testing in schizophrenia and that potential aspects of clinical utility of such testing might include a potential etiological explanation for a patient's condition and reproductive implications for siblings and patients themselves.

REPRODUCTIVE DECISION MAKING

Risk estimates for recurrence of disease in future births can be altered considerably by information from the genetic diagnosis. For example, the average sibling recurrence risk in ASDs is 5%.[3] However, in the case of a dominant single-gene disorder with full penetrance, when a parent is known to carry the pathogenic variant parent, the risk to a future child is 50%. If the disorder is recessive, the sibling risk is 25%. For an x-linked disorder, such as fragile X syndrome, the recurrence risk in a brother is 50%, while a sister may be only mildly affected

but will have a carrier risk of up to 50%. In contrast, if the disorder is the result of a de novo CNV (i.e., not carried by either parent), the sibling risk remains low, at the population average.

Knowledge of recurrence risk is expected to lead to improved quality of life and impact future reproductive decision-making in families affected by DD/ID or ASD associated with specific variants. Several family studies have reported on such measures generally reporting positive results on subjective outcomes assessed.[43, 46, 49, 50]

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF PEDIATRICS

In 2014, the American Academy of Pediatrics (AAP) Committee on Genetics published a clinical report to outline a medical genetic evaluation of children with intellectual disability or global developmental delay.[1] The committee's is as follows:

1. If a specific diagnosis is suspected, arrange for the appropriate diagnostic studies to confirm including single-gene tests or chromosomal microarray test.
2. If diagnosis is unknown and no clinical diagnosis is strongly suspected, begin the stepwise evaluation process:
    a. CMA should be performed in all.
    b. Metabolic testing should be considered and should include serum total homocysteine, acyl-carnitine profile, amino acids; and urine organic acids, glycosaminoglycans, oligosaccharides, purines, pyrimidines, guanidinoacetate/creatine metabolites.
    c. Fragile X testing should be performed in all.
3. If no diagnosis is established:
    a. Male gender and family history suggestive X-linkage, complete XLID panel that contains genes causal of nonsyndromic XLID and complete high-density X-CMA. Consider X-inactivation skewing in the mother of the proband.
    b. Female gender: complete MECP2 deletion, duplication, and sequencing study.

In 2020, the AAP issued a clinical report on identifying infants and young children with developmental disorders through surveillance and screening.[51] 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."

Also in 2020, the AAP published a clinical report on the identification, evaluation, and management of children with autism spectrum disorder which states the following regarding CMA:[52]

> "CMA is recommended if the etiology for developmental disability is not known. CMA identifies copy number variants (CNVs) at this time, which are DNA duplications or

deletions that alter the function of genes. CMA reveals a definitively pathogenic CNV in 5.4% to 14% (median 9%) of individuals with ASD in clinical samples. When CNVs of uncertain significance are included, approximately 17% to 42% of patients with ASD have findings on the CMA. Some of the variants of uncertain significance may be determined as pathogenic in the future."

AMERICAN ACADEMY OF NEUROLOGY AND THE PRACTICE COMMITTEE OF THE CHILD NEUROLOGY SOCIETY

The American Academy of Neurology and the Practice Committee of the Child Neurology Society Evidence Report concludes that "microarray is the genetic test with the highest diagnostic yield in children with unexplained DD/ID" (based on Class III studies).[4] In addition, the report notes that microarray testing can identify only CNVs and is insufficiently sensitive for detecting disorders caused by other mechanisms (e.g., inversions, balanced insertions, polyploidy etc.). Finally, per the report, the often complex results of this testing require confirmation and careful interpretation, often with the assistance of a medical geneticist.[4] 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 AND GENOMICS

In 2011, the American College of Medical Genetics and Genomics (ACMG) published guidelines on array-based technologies and their clinical utilization for detecting chromosomal abnormalities.[53] This was reaffirmed in 2020.[54] The recommendations are based on a limited review of evidence and the findings are from a handful of publications are reported. However, study selection criteria are not included and included publications are not critically appraised. Per the guidelines, CMA testing for copy number variation 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

The guideline warns that the clinicians need to be aware of the "different clinical platforms, the variation in resolution among arrays and information each provides." Also, the guideline notes the limitations of CMA testing (e.g., cannot identify balanced chromosomal rearrangements such as translocations or inversions). Additional ACMG guidelines have been published for the design and performance expectations for clinical microarrays and associated software[17] and for the interpretation and reporting of CNVs,[20] both intended for the post-natal setting.

In 2013 ACMG published guidelines on the genetic evaluation of autism spectrum disorder (ASD), stating that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of ASD is recommended, with the recommendation being for first tier to include FXS and CMA, and second tier to include MECP2 and PTEN testing.[55] 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".

INTERNATIONAL STANDARD CYTOGENOMIC ARRAY CONSORTIUM

The International Standard Cytogenomic Array (ISCA) Consortium published a consensus statement in which they recommend offering CMA as the first-tier genetic test, in place of G-banded karyotype, for patients with unexplained DD/ID, ASDs, or multiple congenital anomalies (MCA).[56] However, the guideline also acknowledges that CMA is still not widely accepted. “Except in special cases, such as those involving family history of multiple miscarriages, a karyotype is not cost effective in a child with DD/ID, ASDs, or MCA and a negative array study. CMA testing is not inexpensive, but the cost is less than the cost of a G-banded karyotype plus a customized FISH test such as subtelomeric FISH, and the yield is greater.”

SUMMARY

Research showing that chromosomal microarray (CMA) or copy number testing can improve health outcomes for patients is limited. However, for certain disorders, CMA test results may provide a diagnosis that leads to changes in medical management and can inform reproductive decision making. In addition, clinical practice guidelines recommend CMA testing for certain groups of patients. Therefore, CMA and copy number testing may be considered medically necessary in individuals with apparent nonsyndromic cognitive developmental delay/intellectual disability, autism spectrum disorder, and/or multiple congenital anomalies.

Most research on chromosomal microarray (CMA) testing has included patients with apparent nonsyndromic cognitive developmental delay/intellectual disability, autism spectrum disorder, and/or multiple congenital anomalies. There is not enough research to show that CMA or copy number testing can improve health outcomes in patients who do not have these disorders, including testing of asymptomatic relatives of patients with abnormal CMA findings. Therefore, CMA or copy number testing is considered investigational when policy criteria are not met.

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CODES

NOTE: The appropriate codes for reporting CMA are 81228 for CMA alone, and 81229 for CMA testing that includes single nucleotide variant (SNV) analysis. It is not appropriate to report code 81422 for CMA.

Codes	Number	Description
CPT	0156U	Copy number (eg, intellectual disability, dysmorphology), sequence analysis
	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
	81479	Unlisted molecular pathology procedure
HCPCS	S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability

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