

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

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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) testing has been proposed for detection of genetic imbalances in infants or children with characteristics of developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), and/or congenital anomalies. CMA testing, including array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) 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 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 may be considered **medically necessary** in children and adolescents (17 years or younger) when any of the following conditions are met:

- 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. Chromosomal microarray analysis is considered **not medically necessary** in children and adolescents when criteria I above is not met.
 - III. Chromosomal microarray analysis is considered **investigational** in adults (18 years of age and older) for the evaluation of any indication.

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

POLICY GUIDELINES

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
 - Conventional testing and outcomes
 - Conservative treatments, if any

CROSS REFERENCES

1. [Preimplantation Genetic Testing](#), 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. [Chromosomal Microarray Analysis \(CMA\) 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 infants or children 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), 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 AND AUTISM SPECTRUM DISORDERS

Children with signs of neurodevelopmental delays or disorders in the first few years of life may eventually be diagnosed with mental retardation or autism syndromes, serious and lifelong conditions that present significant challenges to families and to public health.

Cases of developmental delay/intellectual disability (DD/ID) and of autism spectrum disorders (ASDs) may be associated with genetic abnormalities. For children with clear, clinical symptoms and/or physiologic evidence of syndromic neurodevelopmental disorders, diagnoses are based primarily on clinical history and physical examination, and then may be confirmed with targeted genetic testing of specific genes associated with the diagnosed syndrome. However, for children who do not present with an obvious syndrome, who are too young for full expression of a suspected syndrome, or who may have an atypical presentation, genetic testing may be used as a basis for establishing a diagnosis.

The diagnosis of developmental delay (DD) is reserved for children younger than five years of age who have significant delay in two or more of the following developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living.^[1]

Intellectual disability (ID) is a life-long disability diagnosed at or after age five when intelligence quotient (IQ) testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-V), defines patients with ID as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than two of areas of adaptive behavior or systems of support.

Autism spectrum disorder (ASD) is defined by a persistent impairment in reciprocal social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities. The symptoms of ASD are present from early childhood and limit or impair everyday functioning. Autism spectrum disorder includes disorders previously referred to as early infantile autism, childhood autism, Kanner's autism, high-functioning autism, atypical autism, pervasive developmental disorder not otherwise specified, childhood disintegrative disorder, and Asperger's disorder. Many individuals with ASD also have intellectual impairment and/or language impairment, and some have motor deficits, as outlined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-V), 5th Edition.^[2]

Some children present with features of both DD/ID and of ASDs. For example, Yeargin-Allsopp (2003)^[3] reported that nearly 70% of children with a validated diagnosis of ASDs, sampled from five metropolitan Atlanta counties, had cognitive impairment. The evaluation pathway depends on the pediatrician, consulting specialists, and their consensus on the primary neurodevelopmental diagnosis.

CONGENITAL ANOMALIES

In the United States, congenital anomalies, which occur in approximately 3% of all newborns, are the leading cause of neonatal morbidity and mortality.^[4] Genetic factors have been

identified as an important cause for congenital anomalies. Common chromosomal aneuploidies (e.g., monosomy X, trisomies 21, 18, and 13) have traditionally been diagnosed in the neonatal period using conventional karyotyping. Improved methods, such as fluorescence in situ hybridization (FISH) using chromosome or locus-specific probes, enable the diagnosis of some of the common microdeletion syndromes (e.g., DiGeorge/velocardiofacial syndrome, cri-du-chat syndrome, Prader-Willi and Angelman syndromes). However, FISH is applicable only in patients with a strong clinical suspicion of a specific genetic defect, which may be difficult to detect in a neonate with congenital anomalies, because a patient's clinical presentation may be atypical or have nonspecific phenotypic features that may be shared by several different disorders, or a young patient may lack specific syndromic features that appear at a later age. An improved rate of detection of copy number variants (CNVs) has been shown with the use of aCGH.

GENETIC ASSOCIATIONS WITH DD/ID, ASD, AND CONGENITAL ANOMALIES

DD/ID and ASD may be associated with genetic abnormalities. For children with clear, clinical symptoms and/or physiologic evidence of syndromic neurodevelopmental disorders, diagnoses are based primarily on clinical history and physical examination, and then may be confirmed with targeted genetic testing of specific genes associated with the diagnosed syndrome. However, for children who do not present with an obvious syndrome, who are too young for full expression of a suspected syndrome, or who may have an atypical presentation, genetic testing may be used as a basis for establishing a diagnosis.

Complex autism, which comprises approximately 20% to 30% of cases of autism, is defined by the presence of dysmorphic features and/or microcephaly. Essential autism, approximately 70% to 80% of autism cases, is defined as autism in the absence of dysmorphology. Genetic causes of autism include cytogenetically visible chromosomal abnormalities (5%), single-gene disorders (5%), and CNVs (10%- 20%). Single-nucleotide variant (SNV) microarrays to perform high-resolution linkage analysis have revealed suggestive regions on certain chromosomes not previously associated with autism. The SNV findings in autism, to date, seem consistent with other complex diseases, in which common variation has modest effect size (odds ratio, requiring large samples for robust detection. This makes it unlikely that individual SNVs will have high predictive value.^[5]

Guidelines for patients with ID/DD, ASD, and/or congenital anomalies, such as those published by the American Academy of Pediatrics (AAP)^[6] and the American Academy of Neurology (AAN)^[7] with the Child Neurology Society (CNS), have recommended cytogenetic evaluation to look for certain kinds of chromosomal abnormalities that may be causally related to their condition. The joint AAN and CNS guidelines have noted that only occasionally will an etiologic diagnosis lead to specific therapy that improves outcomes, but suggest the more immediate and general clinical benefits of achieving a specific genetic diagnosis from the clinical viewpoint, as follows:

- “limiting further diagnostic testing”
- “improving understanding of treatment and prognosis”
- “anticipating and managing associated medical and behavioral comorbidities”
- “allowing for counseling regarding risk of recurrence, and preventing recurrence through screening for carriers and prenatal testing.”

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

DIAGNOSTIC TESTING TO DETERMINE GENETIC ETIOLOGY

Most commonly, genetic abnormalities associated with neurodevelopmental disorders are deletions and duplications of large segments of genomic material, called CNVs. For many well-described syndromes, the type and location of the chromosomal abnormality have been established with the study of a large number of cases and constitute a genetic diagnosis; for others, only a small number of patients with similar abnormalities may exist to support a genotype-phenotype correlation. Finally, for some patients, cytogenetic analysis will discover entirely new chromosomal abnormalities that will require additional study to determine their clinical significance.

Conventional methods of cytogenetic analysis, including karyotyping (e.g., G-banded) and FISH, have relatively low resolution and a low diagnostic yield, leaving most cases without identification of a chromosomal abnormality associated with the child's condition.

Chromosomal Microarray

Chromosomal microarray (CMA) is a newer cytogenetic analysis method that increases the chromosomal resolution for detection of CNVs, and, as a result, increases the genomic detail beyond that of conventional methods. CMA results are clinically informative in the same way as results derived from conventional methods, and thus CMA represents an extension of standard methods with increased resolution.

CMA can identify genomic abnormalities that are associated with a wide range of developmental disabilities, including cognitive impairment, behavioral abnormalities and congenital abnormalities. CMA can detect CNVs and the frequency of disease-causing CNVs is highest (20-25%) in children with moderate to severe intellectual disability accompanied by malformations or dysmorphic features. Disease-causing CNVs have been identified in 5-10% of cases of autism, being more frequent in severe phenotypes.^[8]

The term CMA collectively describes two different array platforms: aCGH and SNV arrays. Both types of arrays can identify loss or gain of DNA (microdeletions or microduplications, respectively), known as CNVs.

A portion of the increased diagnostic yield from CMA analysis comes from the discovery that some chromosomal rearrangements that appear balanced (and therefore not pathogenic) by G-banded karyotype analysis are found to have small imbalances with greater resolution. It has been estimated that 40% of apparently balanced de novo or inherited translocations with abnormal phenotype are associated with cryptic deletion if analyzed by CMA.^[9] This contradicts earlier assumptions about inherited, apparently balanced rearrangements and shows that microarray analysis can allow for a less subjective and more accurate interpretation of an abnormal banding pattern.^[10]

REGULATORY STATUS

CMA is commercially available from several laboratories as a laboratory-developed test. Laboratory-developed tests performed by laboratories licensed for high complexity testing

under the Clinical Laboratory Improvement Amendments (CLIA) do not require U.S. Food and Drug Administration (FDA) clearance for marketing.

Recently, the FDA cleared the Affymetrix CytoScan® Dx Assay (Affymetrix, Inc., Santa Clara, CA) for marketing in the United States using the 510(k) approval process.^[11] The test's FDA-cleared indication is for postnatal detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features.

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.

The FDA cleared for marketing the Affymetrix CytoScan® Dx Assay. The FDA reviewed the Affymetrix CytoScan® Dx Assay through its de novo classification process. For the de novo petition, 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.

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 2695 million probes as of July 2017.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature^[12] 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.

CHROMOSOMAL MICROARRAY ANALYSIS

Analytical Validity

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.”^[13]

Several earlier studies (including the 2009 BCBSA TEC Assessment^[14]) have conducted CMA analysis on samples with known chromosomal abnormalities by standard karyotyping. In general, currently available CMA clinical services achieve near 100% sensitivity for known chromosomal abnormalities. False-positive rates (i.e., CNVs of undetermined clinical significance) on known normal samples were inconsistently reported and could not be summarized. One study evaluated the analytic validity of an oligo array and reported 99% sensitivity and 99% specificity with a resolution of 300 to 500 Kb for 10 selected cases with different known chromosomal abnormalities.^[15] However, despite the fact that increased resolution arrays have been quickly translated to clinical services with a resulting increase in diagnostic yield, this has been coupled with an inevitable increase in the potential for results of undetermined significance. Surveys conducted two to three years ago indicated that there is a lack of consensus between laboratories in the interpretation and reporting of CNVs, particularly those that are challenging.^[16] The International Standards for Cytogenomic Arrays (ISCA) Consortium database now offers increased standardization and classification of CNVs that have been previously reported, and should improve consensus in reporting.

Since the analytical validity of CMA has been established, it will no longer be reviewed for new evidence for any indication.

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 several recent 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.^[4,14,17-26] 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^[27,28]; Schaefer and Mendelsohn^[29] 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.^[28]

As noted in the Description section, 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.^[30] Velocardiofacial syndrome is also associated with heart defects.^[31] Klinefelter syndrome may first be detected as developmental delay in early childhood; androgen treatment is an important component of therapy.^[31]

A 2015 TEC Special Report on the use of CMA for the genetic evaluation of patients with DD/ID and ASD found the following for the clinical utility of CMA testing^[13]:

- Studies on the potential impact of CMA on clinical decisions “collectively indicate that identified pathogenic variants can prompt clinical actions potentially impacting morbidity. Less clear is how often outcomes will be improved and in which cases interventions might have occurred in the absence of testing. The proportion that may benefit will depend on the variants identified as well as diagnostic yield, which in turn depends on phenotype severity. Studies did not report on any follow-up or management changes in patients without identified pathogenic variants. In addition to reducing morbidity, bringing closure to a diagnostic odyssey is a reason for genetic testing ... and noted as an outcome in case series and reports. Parents cite obtaining services and support as a reason for testing, but the frequency and can impact on outcomes is difficult to quantify. The studies reviewed convey a set of intermediate outcomes likely to favorably affect the health of some children. Lacking are end-to-end cohort studies following children at presentation to final outcomes.” “There are considerable challenges conducting studies of sufficient size given the underlying genetic heterogeneity, and including follow-up adequate to observe final health outcomes”; however, “studies examining clinical utility have reported intermediate outcomes and indirect evidence.”
- “In addition, outside readily recognizable syndromes, pathogenic variants identified represent a collection of rare disorders. Ascertaining improved net health outcome for rare diseases is not easy. Both conditions and outcomes can be heterogeneous. The evidence reviewed here reflects the accompanying uncertainty, but supports a perspective that identifying a pathogenic variant can: (1) impact the search for a diagnosis, (2) inform follow-up that can benefit a child by reducing morbidity and rarely potential mortality, and (3) affect reproductive planning for parents and later potentially the affected child. There are also likely circumstances where other family members may be impacted owing to the nature of the variant and subsequent cascade (family member) testing. The downsides to testing can include detecting nonpaternity, an incorrect diagnosis, and findings of uncertain significance—how often they occur is uncertain. It is difficult to quantify lower or upper bounds for any potential improvement in the net health outcome owing in part to heterogeneity of disorders, rarity, and outcome importance that may differ according to identified variants. The strong expert

opinion in recommending initial CMA testing over other approaches ... together with the indirect evidence for benefit following testing, supports concluding that the net health outcome can be improved.

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

Prior to the TEC report published by BCBSA in 2015, several large case series were published that reported on management recommendations based on CMA result, including referral to other specialists and further evaluations for potential associated symptoms. These studies ranged from 48 patients (Saam, 2008) to 46,300 patients (Ellison, 2012).^[32-36] Additional clinical action was taken based on CMA result between 45-90% of the time, depending on the study and the indication diagnosed.

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%.^[31] However, if the cause is a dominant single gene disorder with full penetrance and a parent is a carrier, the sibling risk is 50%. If the disorder is recessive but characteristics are otherwise the same, the sibling risk is 25%. If the cause is Fragile X, the recurrence risk in a brother is 50%, while a sister may be only mildly affected but will have a carrier risk of up to 50%. However, in the case of a de novo CNV (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 with children affected with DD/ID or ASD associated with specific variants. Several family studies have reported on such measures generally reporting positive results on subjective outcomes assessed.^[36-39]

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. Therefore, the scientific evidence will no longer be reviewed for CMA testing for children and adolescents for the evaluation of the above indications, as they may be considered medically necessary.

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 5487 patients over 3.5 years.^[40] 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.^[41] 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.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF PEDIATRICS

In 2014, the American Academy of Pediatrics Committee on Genetics published a clinical report to outline a medical genetic evaluation of children with intellectual disability or global developmental delay.^[6] 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/creatinine 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.

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).^[7] 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.^[7] 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.^[42] The recommendations are based on a limited review of evidence and the findings 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^[43] and for the interpretation and reporting of CNVs,^[44] 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.^[45] 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).^[46] 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 for chromosomal microarray (CMA) testing in children or adolescents is limited. However, testing may improve health outcomes and improve diagnostics. In addition, practice guidelines recommend CMA testing for defined populations. Therefore, CMA may be considered medically necessary in pediatric and adolescent individuals when policy criteria are met. When the policy criteria are not met, CMA testing is considered not medically necessary.

There is not enough research to show that chromosomal microarray (CMA) testing in adults improves health outcomes for any indication. No clinical guidelines based on research recommend CMA testing in adults. Therefore, CMA testing in adults is considered investigational for any indication.

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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 polymorphism (SNP) analysis. It is not appropriate to report code 81422 for CMA.

Codes	Number	Description
CPT	81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
	81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for 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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