Medical Coverage Policy

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Comparative Genomic Hybridization (CGH)/Chromosomal Microarray Analysis (CMA) for Selected Hereditary Conditions

Table of Contents

Related Coverage Resources

Autism Spectrum Disorders/Pervasive Developmental Disorders: Assessment and Treatment
Genetics
Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis
Molecular and Proteomic Diagnostic Testing for Hematology and Oncology Indications

Overview

This Coverage Policy addresses germline genetic testing using comparative genomic hybridization (CGH)/chromosomal microarray analysis (CMA) and low-pass whole genome sequencing for selected post-natal, non-oncological indications, including unexplained developmental delay, autism spectrum disorder, intellectual disability, multiple congenital anomalies, and developmental and epileptic encephalopathy.

Coverage Policy

Many benefit plans limit coverage of genetic testing and genetic counseling services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

Comparative genomic hybridization (CGH)/chromosomal microarray analysis (CMA) for reproductive and prenatal indications is discussed in Cigna Medical Coverage Policy Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis. For testing of hematology and oncology-related indications, please see Cigna Medical Coverage Policy Molecular and Proteomic Diagnostic Testing for Hematology and Oncology Indications.

Genetic Counseling

Medically Necessary

Pre- and post-test genetic counseling is recommended for any individual undergoing genetic testing for any indication.

Pre-and post-test genetic counseling is considered medically necessary for EITHER of the following:

- an individual undergoing genetic testing

- an individual who is a potential candidate for genetic testing

by ANY of the following:

- an independent Board-Certified or Board-Eligible Medical Geneticist
- an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
- a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APNG) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

Comparative Genomic Hybridization (CGH) / Chromosomal Microarray Analysis (CMA) and Low-Pass Whole Genome Sequencing

Comparative genomic hybridization (CGH)/chromosomal microarray analysis (CMA) or low-pass whole genome sequencing (low-pass WGS) is considered medically necessary for ANY of the following indications:

- autism spectrum disorder in which the phenotypic characteristics of a specific genetic disorder are absent
- non-syndromic global developmental delay or intellectual disability in which the phenotypic characteristics of a specific genetic disorder are absent
- multiple congenital anomalies not specific to a well-delineated genetic syndrome
- one major anomaly and clinical suspicion for a syndrome caused by a copy number variant (e.g., 22q11.2 deletion syndrome)
- known or suspected developmental and epileptic encephalopathy (characterized as onset before three years of age) for which likely non-genetic causes of epilepsy (e.g., environmental exposures; brain injury secondary to complications of extreme prematurity, infection, or trauma) have been excluded
- biological parent of a fetus/child with an equivocal or positive CGH/CMA or low-pass WGS result

Repeat CGH/CMA or low-pass WGS is considered medically necessary when ALL of the following criteria are met:

- Medical necessity for testing is established based on the criteria noted above.
- Results of repeat testing will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
- Testing method is considered scientifically valid for identification of the genetic abnormality, disorder or syndrome.
- Request for testing uses a methodology not previously employed in testing of the individual.

Not Medically Necessary

CGH/CMA or low-pass WGS for the purposes of genetic testing in the general population is considered not medically necessary.

General Background

Genetic Counseling

Genetic counseling is the process of helping individuals understand and adapt to the medical, psychological, and familial indications of genetic contributions to disease. Genetic counseling services span the life cycle from preconception counseling to infertility evaluation, prenatal genetic screening and diagnosis, and include predisposition evaluation and genetic diagnosis. Genetic counseling is recommended both pre-and post-genetic test to interpret family and medical histories to assess the chance of disease occurrence and recurrence, educate regarding inheritance, testing, management prevention and resources, and counsel to promote informed choices and adaptation to risk or condition. Germline and somatic genetic testing may identify secondary and incidental findings unrelated to the primary testing indication. Pre-test genetic counseling can elicit patient preferences regarding these findings, and assist in formulating a plan for returning such results before testing occurs (National Society of Genetic Counselors [NSGC], 2020).

A variety of genetics professionals provide these services: board-certified or board-eligible medical geneticists, an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor, and genetic nurses credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APNG) by either the Genetics Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC).

Comparative Genomic Hybridization (CGH)/Chromosomal Microarray Analysis (CMA)

Cytogenetic testing analyzes cells in a sample of blood, tissue, bone marrow, or amniotic fluid to look for changes in chromosomes. Conventional cytogenetic tests identify known genetic abnormalities when a specific clinical syndrome is suspected. Such testing is used to identify balanced rearrangements (e.g., translocations or inversions), alterations in chromosome structure, sequence alterations, copy number changes (deletion, duplication and amplification), single-base pair mutation, 20% or lower level of mosaicism, and some types of polyploidy, including triploidy and tetraploidy.

A microarray is a laboratory test platform that allows rapid analysis of thousands of different deoxyribonucleic acid (DNA) sequences. Comparative genomic hybridization (CGH)/chromosomal microarray analysis (CMA), also known as molecular karyotyping, is a form of array-based technology that has been proposed as an alternative to conventional cytogenetic testing for a number of indications, including autism spectrum disorders, global developmental delay, intellectual disability, unspecified congenital anomalies and known or suspected developmental and epileptic encephalopathy (characterized as onset before three years of age).

CGH/CMA compares a test sample of an individual's DNA against a normal control sample. It can identify submicroscopic genomic copy number variants (CNVs), such as deletions and duplications, when a specific genetic disorder has not been identified by conventional cytogenetic testing. Whole genome array, also known as array CGH (aCGH), has a wider coverage over the entire human genome and can discover new CNVs of unknown clinical significance. For developmental delay, intellectual disability, multiple congenital anomalies, and/or autism spectrum disorder, CGH/CMA has a diagnostic yield 15-20% greater than that of traditional karyotype analysis (Wallace and Bean, 2020).

A limitation of CGH/CMA is that in contrast to conventional cytogenetic tests, it cannot identify balanced rearrangements (e.g., translocations or inversions), alterations in chromosome structure that are not represented on the array, sequence alterations, single-base pair mutation, mosaicism ≤ 10-20%, and some types of polyploidy, including triploidy and tetraploidy. Its false positive rate has been reported to be as high as 7%. When CGH/CMA identifies a CNV of known clinical significance, conventional testing is typically used to confirm the findings.

If an unknown CNV is detected, a genomic database is checked to see if the abnormality has been previously reported and whether or not it has been previously associated with a benign or disease-related condition. One example of a CNV disorder is DiGeorge syndrome (22q11.2 deletion syndrome). People with DiGeorge syndrome may present with congenital heart disease, palatal abnormalities, immune deficiency, hearing loss, and learning difficulties, among other conditions. The syndrome is diagnosed when a heterozygous deletion is identified at chromosome 22q11.2 on chromosomal microarray analysis (McDonald-McGinn, et al., 2020). Evaluation of parental samples is sometimes performed to determine if the abnormality is inherited or is a de

novo mutation (a spontaneously-occurring genetic alteration that was not inherited). CNVs that appear in normal individuals have been reported to be as high as 12%, making diagnostic interpretation and identification of CNVs' clinical significance difficult. Various chromosomal microarray platforms are currently being used and no one platform has been found to be clearly superior to all of the others for clinical purposes (Schaefer and Mendelsohn, 2013; Miller, et al., 2010; Pickering, et al., 2008; Burton, 2006).

Low-pass Whole Genome Sequencing
Low-pass whole genome sequencing (WGS) is an attenuated version of standard WGS, which sequences to a read depth of 20x-40x. In low-pass WGS, lower read depths are used (e.g., 5x, 2x, <1x), yielding a lower level of resolution of results (Chaubey, et al., 2020). Although exact definitions have varied, the American College of Medical Genetics and Genomics (ACMG) has denied low-pass WGS as a read depth of 15x or less (Raca, et al., 2023). The lower read depth does not allow for accurate detection of sequencing errors (e.g., single-nucleotide variants [SNVs]), but is able to detect many copy number variants (CNVs). The lower read depth also allows for lab efficiency in being able to process more samples at a time. Low-pass WGS has shown similar diagnostic yield and potentially enhanced resolution for CNV detection compared with CMA testing in the prenatal and postnatal settings (Chau, et al., 2020; Chaubey, et al., 2020; Wang et al., 2020).

When evaluating genetic tests, including CGH/CMA and low-pass WGS, three factors are considered: analytical validity, clinical validity, and clinical utility.

- **Analytical validity** refers to how well the test detects the presence or absence of a genetic variation (i.e., the accuracy of the test).
- **Clinical validity** refers to how well the genetic variant(s) being examined is related to the presence, absence, or risk of a specific disease or condition.
- **Clinical utility** refers to whether the test can help guide clinical management (i.e., the diagnosis, treatment, management, or prevention of a disease).

Laboratories that perform genetic testing are subject to federal regulatory standards (Clinical Laboratory Improvement Amendments [CLIA]), which control the quality of lab practices. As such, available genetic tests have a high degree of analytical validity. However, CLIA standards do not address the clinical validity or the clinical utility of genetic tests. False positives and false negatives do occur, and interpretation of the results can be challenging. For some disorders, genetic testing may be possible, but the results do not help with a diagnosis or lead to improved health outcomes. Conversely, if the diagnosis is already apparent, genetic testing may not be necessary (National Human Genome Research Institute [NHGRI], 2022; Lee, 2020).

Autism Spectrum Disorder, Global Developmental Delay, and Intellectual Disability
Approximately one in 44 children in the United States has been identified with autism spectrum disorder (ASD) (Centers for Disease Control and Prevention [CDC], 2022). ASD is four times more common in males than in females, and more prevalent in white children compared to Black or Hispanic children (1.1 and 1.2 times more prevalent, respectively). Black and Hispanic children are less likely to be identified with ASD than white children, suggesting that Black and Hispanic children may face socioeconomic or other barriers (e.g. stigma, non-English primary language, non-citizenship) that lead to a lack of or delayed access to evaluation, diagnosis, and services. However, the CDC has reported that the differences in ASD identification among white, Black, and Hispanic children have been getting smaller over time. These reduced differences may be due to more effective outreach directed toward minority communities and efforts to have all children screened for ASD (CDC, 2019).

Developmental delay typically refers to a child under six years old who presents with delays in the attainment of developmental milestones at the expected age and demonstrates deficits in learning and adaptation. Global developmental delay involves a significant delay in two or more developmental domains, including gross/fine motor, speech/language, cognition, social/personal, and activities of daily living. The delays may be significant and predictive of the development of cognitive and/or intellectual disability (Satya-Murti, et al., 2015; Moeschler, et al., 2014).

According to the American Association on Intellectual and Developmental Disabilities (AAIDD), intellectual disability is characterized by significant limitations both in intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills. This disability starts before the age of 22. Generally, the

individual has an intelligence quotient (IQ) score of below 70–75 and is compromised in the areas of conceptual skills, social skills, and practical skills (AAIDD, 2022). Intellectual disability can be caused by genetic abnormalities seen in various syndromes such as: Down syndrome, Edwards syndrome, Patau syndrome, Fragile X syndrome, Rett syndrome, Angelman syndrome or Prader-Willi (Prader-Labhart-Willi) syndrome.

Congenital Anomalies
Congenital anomalies, or birth defects, are anatomic abnormalities present at birth which may present in various patterns, and are usually multifactorial. In 10–15% of cases, anomalies can be attributed to chromosomal abnormalities. Examples of congenital anomalies include: cleft palate; clubfoot; spina bifida; vision and hearing impairments; and respiratory, renal and cardiac malformations. Congenital anomalies may be coupled with intellectual disability and global developmental delay (Husain and Koo, 2021).

The clinical utility of CGH/CMA testing has been established for genetic evaluation of an individual diagnosed with autism spectrum disorder, global developmental delay and intellectual disability in which the phenotypic characteristics of a specific genetic disorder are absent, and/or when multiple or unspecified congenital anomalies are not specific to a well-delineated genetic syndrome.

Developmental and Epileptic Encephalopathy
A genetic etiology is able to be identified in approximately 40% of epilepsy cases; however, genetic testing currently plays a limited role in clinical care and management for most cases. The study of epilepsy genetics is complicated by factors such as variable expressivity, variable penetrance and complex inheritance. Only 1-2% of cases are inherited as a single gene disorder (Michelucci, et al., 2012). In addition, the currently available genetic testing for epilepsy syndromes only identifies causative mutations in a minority of families (Ottman, et al., 2010). Overall, the utility of genetic testing and scope of testing is dependent upon the particular epilepsy phenotype. Other potential causes of epilepsy (e.g., acquired structural etiologies such as trauma or infection; environmental exposures) are typically explored prior to or alongside genetic testing (Scheffer, et al., 2017).

Genetic testing has been suggested for epileptic encephalopathies, as many genes that have been associated with the condition have been determined to be actionable (Weber, et al., 2017). Epileptic encephalopathies refer to epilepsy which is seen in association with developmental/cognitive delay and/or regression. Diagnostic criteria for developmental and epileptic encephalopathy are generally made based on observations on electroencephalography (EEG), imaging, and seizure semiology. There is significant clinical and genetic heterogeneity in this group of conditions. Diagnosis at an early age is particularly difficult as the full phenotypic expression may not yet be known. Varying electroclinical syndromes are defined by International League Against Epilepsy (ILAE) criteria and many have overlapping or heterogeneous genetic causes (Palmer, et al., 2018). When the developmental and epileptic encephalopathy is ultimately determined to be attributed to a specific gene, the specific terminology will be used (e.g., STXBP1 encephalopathy; KCNQ2 encephalopathy) (Scheffer, et al., 2017).

Developmental and epileptic encephalopathy (DEE) refers to a group of epilepsies which are characterized by seizures and developmental delay, or even loss of developmental skills. DEE is a severe presentation in which there is an underlying cause contributing to the developmental delay, in addition to frequent seizures which may substantially worsen developmental problems. Improvement in seizure control may in turn have the potential to improve the developmental consequences of the disorder, however the developmental encephalopathy component will not change (Scheffer, et al., 2017).

When an epileptic encephalopathy is known or suspected in an infant or a young child, broad testing such as CGH/CMA is often indicated for timely diagnosis and appropriate clinical management. If a specific syndrome is not readily identified, CMA is a reasonable first line diagnostic measure for those with known or suspected early epileptic encephalopathy (characterized by onset before three years of age). The clinical utility of testing for epilepsy includes: provision of additional information leading to family reassurance, guidance for family planning, early identification of special needs, avoidance of ongoing diagnostic assessment where no clear diagnosis exists, predicted prognosis for the patient, pharmacotherapy and identification of medical risk and the need for ongoing monitoring.

U.S. Food and Drug Administration (FDA)

In August 2017, the FDA granted 510(k) Class II approval to the GenetiSure Dx Postnatal Assay (Agilent Technologies, Inc., Santa Clara, CA). The predicate device was the CytoScan® Dx Assay (Affymetrix, Inc., Santa Clara, CA). In January 2014, the FDA had approved the de novo request for reclassification of the CytoScan® Dx Assay from class III to class II, as a postnatal chromosomal copy number variation detection system.

Approval by the FDA for array comparative genomic hybridization (CGH) tests is not required. CGH is a laboratory-developed test performed by various Clinical Laboratory Improvement Amendments (CLIA)-licensed laboratories. Array platforms, assay protocol, and analysis systems vary from laboratory to laboratory.

On April 19, 2022, the FDA issued a safety communication warning patients and healthcare providers of the risk of false results with genetic non-invasive prenatal screening tests (NIPS or NIPT). NIPT analyzes small fragments of fetal DNA circulating in the pregnant woman's blood to determine the risk that the fetus will be born with certain genetic abnormalities. While trisomies 13, 18 and 21 are detected with high accuracy, NIPT for other conditions or for microdeletions is not widely supported. The FDA communication noted that no NIPS tests have yet been authorized, cleared, or approved by the agency, and that the tests may give false results, such as reporting a genetic abnormality when the fetus is not actually affected (i.e., a “false positive” result). The FDA recommended patients talk with a genetic counselor or other healthcare provider before and after testing, and not use the results of screening tests like NIPT alone to diagnose chromosomal abnormalities or disorders, or to make decisions about medical care. The communication noted the importance of performing confirmatory diagnostic testing to determine whether or not the fetus truly has a chromosomal abnormality following a positive screening test result.

Literature Review

Autism Spectrum Disorder (ASD): Several clinical studies have demonstrated the benefit of CGH/CMA to aid in clinical management of ASD. Siu et al. (2016) reported outcomes of a small prospective study involving 68 adults and children ASD. Fifteen copy number variants (CNVs) were detected and eight of them were clinically significant. The overall diagnostic yield was 11.8 %. Diagnostic yields in the adult and pediatric groups were 12.2% and 11.1%, respectively.

Shen et al. (2010) evaluated 933 patients with a predominant diagnosis of autistic disorder (n=477) and pervasive developmental disorder-not otherwise specified (PDD-NOS) (n=454) to compare the outcomes of karyotype testing, array CGH (aCGH) and Fragile X testing. A greater number of individuals diagnosed with intellectual disability, dysmorphic features, and seizure disorders had abnormalities detected by aCGH compared to those identified by karyotype or Fragile X testing. Ninety-five abnormalities were considered variants of uncertain significance. Fifty of the abnormalities noted on aCGH were below the size range detected by karyotype. Although aCGH detected more abnormalities, the authors noted that aCGH could not replace a G-banded karyotype in this population because of the inability of aCGH to detect balanced rearrangements. The impact of aCGH results on clinical management decisions for this patient population was not discussed. Limitations of the study noted by the authors include concerns regarding credibility of diagnosis and bias regarding ascertainment of patients through tertiary care centers.

To determine the benefit of CGH as a diagnostic tool, Jacquemont et al. (2006) conducted whole-genome CGH using a one megabase (Mb) resolution (Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK) on 29 patients with idiopathic syndromic ASD. The patients had normal high-resolution karyotype (approximately 800 bands), biochemical tests and hematological results prior to CGH testing. Thirty-three chromosome gains or losses in 22 patients were identified by CGH. Twenty-three variants were considered normal. The ten remaining abnormalities were considered possibly pathogenic and were validated by at least one independent method. CGH identified eight clinically relevant abnormalities in 27.5% of the patients.

Global Developmental Delay, Intellectual Disability and Congenital Anomalies: Several prospective and retrospective studies and systematic reviews/meta-analyses have evaluated the clinical utility of CGH/CMA testing for the diagnosis and clinical management of individuals with developmental delay, intellectual disability and congenital anomalies (McCormack, et al., 2016; Bartnik, et al., 2014; Chong, et al., 2014; Lee, et al., 2013; Ellison, et al., 2012; Hayashi, et al., 2011; Sagoo, et al., 2009; Pickering, et al., 2008; Shao, et al., 2008; Shevell, et al., 2008; Baris, et al., 2007; Engels, et al., 2007; Subramonia-Iyer, et al., 2007; Wong, et al., 2005). Various microarray platforms were used in these studies. Study limitations included a heterogeneous patient population,

variability in study design, variation in the microarray used for testing and high false positive rate, (up to 7% in the study by Subramonia-Iyer et al.). The diagnostic yield of causal genetic abnormalities detected by CGH ranged from 10-20%, as reported by the systematic reviews. In the study by Ellison et al., 35% of all pathogenic copy number changes warranted further clinical action. Data suggest that CGH is an acceptable option for this subpopulation when other conventional cytogenetic tests are negative.

Developmental and Epileptic Encephalopathy: Chromosomal microarray (CMA) has been found to have diagnostic yields in the approximately 5–30% range in various studies in epilepsy (Noh, et al., 2012). Specific to epileptic encephalopathies, array comparative hybridization (aCGH) has been reported to identify copy number variants in ~4-13% with further confirmed de novo and pathogenic variants in 2.9-13% (Epilepsy Phenome/Genome Project & Epi4K Consortium, 2015; Mercimek-Mahmutoglu, et al., 2015). A study by Berg et al. (2017) found that in patients presenting with early life epilepsies 32/188 (17%) had diagnostic/pathogenic findings on CMA. In the SCN1A gene specifically, deletions and duplications have been identified in 8-27% of individuals (Miller, et al., 2022). Other groups have found similar yields (Tumiene, et al., 2018; Poduri, 2017; Allen, et al., 2015; Olson, et al., 2014; Mefford, et al., 2011). This rate is similar to diagnostic rates for autism spectrum disorder (10%) as noted by the American College of Medical Genetics and Genomics (ACMG) (Schaefer and Mendelsohn, 2013).

Parental Testing
Parental testing via CGH/CMA is supported by published consensus guidelines by the American College of Medical Genetics and Genomics. On behalf of the ACMG, Manning and Hudgins (2020) noted that appropriate follow-up testing includes parental testing when chromosomal imbalances are detected by CMA.

Repeat Testing
As microarray technology has continued to evolve there have been improvements in the ability to detect chromosomal changes not previously identified when using a CMA testing platform with lower resolution. Repeat testing may be appropriate in selected individuals if medical necessity is established based on criteria noted in this Coverage Policy and results of the testing will directly impact clinical decision-making and management of the individual being tested. The proposed test should be scientifically validated to identify a genetic abnormality, disorder or syndrome and should not have previously been used for testing of the individual.

Professional Societies/Organizations
American Academy of Pediatrics (AAP): In 2020, the AAP published a clinical report on the identification, evaluation, and management of children with autism spectrum disorder (ASD). As part of the etiologic workup for ASD, the AAP advocated that a genetic evaluation be offered and recommended to the family. Identifying a genetic etiology may provide information regarding prognosis, co-occurring conditions, and familial recurrence risk, as well as identify resources and avoid unnecessary testing. The AAP advocated that chromosomal microarray (CMA) was the most appropriate initial laboratory test, followed by more targeted testing if a specific syndrome or metabolic disorder was suspected (e.g. fragile X syndrome). If history and physical exam, CMA, and fragile X (or other syndrome) testing did not identify an etiology, whole exome sequencing may be considered (Hyman, et al., 2020).

The 2014 AAP guidance for the clinical genetic evaluation of children with intellectual disability and developmental delays notes that chromosome (genomic) microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology. If a diagnosis is unknown and no clinical diagnosis is strongly suspected, providers should begin the stepwise evaluation process; chromosomal microarray should be performed in all (Moeschler and Shevell, 2014).

American Academy of Neurology (AAN): On behalf of the AAN, Satya-Murti et al. (2015) published a model coverage policy for chromosomal microarray analysis for intellectual disabilities. The document notes the criteria do not represent a binding standard of care and that the criteria are proposed as clinical contexts that readily support the use of microarray testing.

Per the AAN, chromosomal microarray analysis is reasonable and medically necessary for diagnosing a genetic abnormality when all of the following conditions are met:

- In children with developmental delay/intellectual disability (DD/ID) or an autism spectrum disorder (ASD) according to accepted Diagnostic and Statistical Manual of Mental Disorders-IV criteria

AND:

- If warranted by the clinical situation, biochemical testing for metabolic diseases has been performed and is negative
- Targeted genetic testing, (for example: FMR1 gene analysis for Fragile X), if or when indicated by the clinical and family history, is negative
- The results for the testing have the potential to impact the clinical management of the patient
- Face-to-face genetic counseling with an appropriately trained and experienced healthcare professional has been provided to the patient (or legal guardian[s] if a minor child); patient or legal guardians have given their consent for testing; cognitively competent adolescent patients have given their assent for testing as well.

The guideline noted the presence of major and minor congenital malformations and dysmorphic features should be considered evidence that microarray testing will be more likely to yield a diagnosis. However, dysmorphic and syndromic features are not required for testing.

Limitations of testing include the following:

- Absence of an appropriate and informed consent from the patient, a parent (in case of minors) or a guardian (in persons with cognitive impairment) is necessary prior to testing.
- Inadequacy of knowledge about the test and the actions required to address the results of the test.
- A lack of clear value for chromosomal microarray analysis in all instances other than those delineated above. Under these circumstances the test is considered investigational.
- Chromosomal microarray analysis would not be considered medically necessary when a diagnosis of a disorder or syndrome is readily apparent based on clinical evaluation alone.

American College of Medical Genetics and Genomics (ACMG): In its clinical practice resource on array-based technology for the detection of chromosomal abnormalities, ACMG recommended the following:

- CMA testing for copy number variations (CNV) is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:
  - multiple anomalies not specific to a well-delineated genetic syndrome
  - apparently nonsyndromic developmental delay/intellectual disability
  - autism spectrum disorders
- Further determination of the use of CMA testing for the evaluation of the child with growth retardation, speech delay, and other less well-studied indications is recommended, particularly by prospective studies and aftermarket analysis.
- Appropriate follow-up is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/fluorescence in situ hybridization (FISH) studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.

ACMG noted that clinicians ordering the test need to be aware of the different clinical platforms (e.g., BAC versus oligo, targeted versus whole genome, and SNP), the variation in resolution among arrays and the information each provides. The limitations of aCGH include the inability to identify balanced chromosomal rearrangements (e.g., translocations, inversions), or differentiate free trisomies from unbalanced Robertsonian translocations. The ACMG also noted some aneuploidies and marker chromosomes may be missed; the accuracy of detecting low levels of mosaicism has been questioned; interpretation of the significance of a rare copy number change can be incomplete; and that triploidy will not be detected by some forms of microarray. According to ACMG, the clinician should understand what type of follow-up tests will be performed, and on whom, in the event of abnormal results. Further, for deletions and duplications, parental studies (by FISH or metaphase preparations, if possible) should be conducted to rule out the presence of a chromosomal rearrangement such as an insertion or inherited duplication (Manning and Hudgins, 2020).

In 2023, the ACMG published a statement regarding points to consider in detecting germline structural variants using next generation sequencing. Per ACMG, low-pass whole genome sequencing (WGS) shows similar diagnostic yield and possible enhanced resolution for CNV detection compared with CMA testing in the postnatal and prenatal clinical settings (Raca, et al., 2023). One caveat is that it does not readily allow for triploidy detection and performs to a lesser degree in detecting loss of heterozygosity (LOH). When these two variant types are not likely clinically relevant, low-pass WGS is a reasonable option for CNV detection.

The 2013 guideline update for genetic evaluation for autism spectrum disorders (ASDs) lists CMA (oligonucleotide array-comparative genomic hybridization or single-nucleotide polymorphism array) as a first tier diagnostic test for the evaluation of ASDs. If the individual has a recognizable syndrome firmly documented as associated with ASDs (e.g., Angelman syndrome, Fragile X syndrome), further investigation into the etiology is not necessary. For genetic conditions that have been reported in association with ASDs for which the reported association is not convincing, ACMG recommends that an etiologic evaluation of the ASD be conducted, including CGH (Schaefer and Mendelsohn, 2013).

American Academy of Neurology (AAN)/Child Neurology Society (CNS): A systematic review was conducted to determine the diagnostic yield of genetic and metabolic evaluation of children with global developmental delay or intellectual disability (GDD/ID). In their recommendations for future research, AAN/CNS (2011) noted that research is lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis in this population, and the ability to rate diagnostic tests on the basis of factors other than diagnostic yield, such as the availability of effective treatment, would have a positive influence on clinical practice.

Use Outside of the US
European Society of Child and Adolescent Psychiatry (ESCAP): The ESCAP practice guidance for the diagnosis and treatment of autism recommended that basic assessment should include family history (three-generation); physical examination; CMA analysis, or karyotyping if CMA is not available; screening for pathogenic mutations in the MECP2 gene; Fragile X testing in males, and in females if indicated by family history and/or phenotype; and PTEN gene analysis if other symptoms suggest that such testing is warranted (Fuentes, et al., 2021).

National Institute for Health and Care Excellence (NICE): In updated guidance on the diagnosis of autism spectrum disorder, NICE advised against routine genetic testing as part of the diagnostic assessment. Rather, NICE advocated genetic testing on an individual basis if specific dysmorphic features, congenital anomalies and/or evidence of an intellectual disability were observed, and as recommended by a regional genetics center. NICE noted that more genetic abnormalities in autism are being identified, but their causal role in autism is not clear. Currently, the yield of abnormal genetic results using comparative genomic hybridization (CGH) array is reported to be higher in individuals with dysmorphic features and/or intellectual disability. NICE noted that it is important to have a better understanding of the diagnostic yield of CGH array testing before extending it to a wider population. It is also essential to identify any negative consequences that may result from routine testing (NICE, 2017; 2021).

International League Against Epilepsy (ILAE): ILAE guidelines suggest that genetic evaluation for Dravet syndrome and other infantile-onset epileptic encephalopathies should be available at a tertiary and quaternary level of care (level C), and that the genetic testing strategy can vary according to suspected underlying condition affecting the infant (Wilmshurst, et al., 2015).

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No Determination found	
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
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
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

HCPCS Codes	Description
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability

References

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