

Summary

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 increases the diagnostic yield over karyotyping in this population and may impact clinical management decisions. Next-generation sequencing (NGS) panel testing allows for simultaneous analysis of a large number of genes and has been proposed as a way to identify single-gene causes of syndromes that have autism as a significant clinical feature, in patients with normal CMA testing.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Lab tests for chromosomal microarray testing and next-generation sequencing are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

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

On January 17, 2014, the Affymetrix CytoScan® Dx Assay was cleared for marketing by FDA through the de novo classification process. For the de novo petition, FDA’s review of the CytoScan® Dx Assay included an analytic evaluation of the test’s ability to accurately detect numerous chromosomal variations of different types, sizes, and genome locations compared with several analytically validated test methods. FDA found that the CytoScan® Dx Assay could analyze a patient’s entire genome and adequately detect chromosome variations in regions of the genome associated with intellectual and developmental disabilities. FDA product code: PFX.

POLICY STATEMENT

Chromosomal microarray analysis may be considered medically necessary as first-line testing in the initial postnatal evaluation of individuals with any of the following:

Apparently nonsyndromic developmental delay/intellectual disability

Autism spectrum disorder

Multiple congenital anomalies not specific to a well-delineated genetic syndrome.

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

POLICY GUIDELINES (IF NEEDED)

A 2013 guidelines update from American College of Medical Genetics stated that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of autism spectrum disorder is recommended, with the recommendation being for first tier to include fragile X syndrome and chromosomal microarray (CMA) testing.

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

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Commercially Available Tests

CMA Analysis

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

Affymetrix CytoScan Dx has been cleared by the U.S. Food and Drug Administration (FDA) through the de novo 510(k) process. FDA’s review of the CytoScan Dx Assay included an analytic evaluation of the test’s ability to accurately detect numerous chromosomal variations of different types, sizes, and genome locations compared with several analytically validated test methods. 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 ID/DD. Reproducibility decreased with the CNV gain or loss size, particularly when less than approximately 400 kilobases (kb; generally recommended as the lower reporting limit).

FirstStepDx PLUS (Lineagen, Salt Lake City, UT) uses Lineagen’s custom-designed microarray platform manufactured by Affymetrix. This microarray consists of 1,953,246 unique nonpolymorphic probes and 743,304 SNP probes that come standard on the Affymetrix CytoScan HD® microarray, with an additional 83,443 custom probes designed by Lineagen.

Ambry Genetics (Aliso Viejo, CA) offers multiple tests (CMA and NGS) that are designed for ASD and neurodevelopmental disorders.

LabCorp offers the Reveal SNP Microarray-Pediatric for individuals with nonsyndromic congenital anomalies, dysmorphic features, DD/DD, and/or ASD.

Next-Generation Sequencing

A variety of commercial and academic laboratories offer NGS panels designed for the evaluation of ASD, DD/ID, and congenital anomalies, which vary in terms of the numbers of and specific genes tested.

Courtagen (Woburn, MA) offers 3 NGS panels intended for the assessment of developmental and behavioral phenotypes:

- devSEEK® Triome™: includes 1119 genes associated with DD/ID and ASD.
- devSEEK®: includes 237 genes associated with DD/ID and ASD, with additional testing available for large deletions and duplications.
- devACT® Clinical Management Panel: includes 250 genes associated with DD/ID and ASD, focusing on genes associated with actionable clinical management changes, with additional testing available for large deletions and duplications.

Emory Genetics Laboratory offers an NGS ASD panel of genes targeting genetic syndromes that include autism or autistic features.

Greenwood Genetics Center (Greenwood, SC) offers an NGS panel for syndromic autism that includes 83 genes.

**BENEFIT APPLICATION**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

**RATIONALE**

**Summary of Evidence**

For individuals who have developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive chromosomal microarray (CMA) testing, the evidence includes primarily case series. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. The available evidence supports test accuracy and validity. Although systematic studies of the impact of CMA on patient outcomes are lacking, the improvement in diagnostic yield over karyotyping has been well-demonstrated. While direct evidence of improved outcomes with CMA compared with karyotyping is lacking, for at least a subset of the disorders potentially diagnosed with CMA in this patient population, there are well-defined and accepted management steps associated with positive test results. Further, there is evidence of changes in reproductive decision making as a result of positive test results. The information derived from CMA testing can: end a long diagnostic odyssey, result in a reduction in morbidity for certain conditions with initiation of surveillance or management of associated comorbidities, and may impact future reproductive decision making for parents and potentially the affected child. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have DD/ID, ASD, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive next-generation sequencing (NGS) panel testing, the evidence includes primarily case series. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, morbid events, and resource utilization. The rates of variants of uncertain significance associated

with NGS panel testing in this patient population are not well-characterized. The yield of testing and likelihood of an uncertain result is variable, based on gene panel, gene tested, and patient population. There are real risks of uninterpretable and incidental results. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Academy of Pediatrics

In 2014, the American Academy of Pediatrics (AAP) issued a clinical report on the optimal medical genetics evaluation of a child with or global developmental delays (GDD) or ID. Regarding CMA testing, this report states: “CMA now should be considered a first tier diagnostic test in all children with GDD/ID for whom the causal diagnosis is not known… CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies.”

American Academy of Neurology and Child Neurology Society

In 2011, the American Academy of Neurology and the Child Neurology Society updated their guidelines on the evaluation of unexplained global DD/ID with information on genetic and metabolic (biochemical) testing to accommodate advances in the field. The guidelines concluded that CMA testing has the highest diagnostic yield in children with DD/ID, that the “often complex results require confirmation and careful interpretation, often with the assistance of a medical geneticist,” and that CMA should be considered the “first-line” test. The guidelines acknowledged that “Research is sorely lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis.”

American College of Medical Genetics

The American College of Medical Genetics (ACMG) published guidelines on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. CMA testing for copy number variant (CNV) is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

A. Multiple anomalies not specific to a well-delineated genetic syndrome
B. Apparently nonsyndromic developmental delay/intellectual disability
C. ASD.

Additional ACMG guidelines have been published on the design and performance expectations for clinical microarrays and associated software and for the interpretation and reporting of CNVs, both intended for the postnatal setting. A 2013 update included recommendations for validation of microarray methodologies for both prenatal and postnatal specimens.

A 2013 guideline revision from ACMG states 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 fragile X syndrome and CMA, and second tier to include MECP2 and PTEN testing. The guideline states that “this approach will evolve with continued advancements in diagnostic testing and improved understanding of the ASD phenotype. Multiple additional conditions have been reported in association with an ASD phenotype, but none of these has been evaluated in a large prospective cohort. Therefore, a future third tier of evaluation is a distinct possibility. Further studies would be needed to elevate the evidence to the point of recommended testing. Alternatively, advances in technology may permit bundling of individual tests into an extended, more readily accessible, and less expensive platform. The accumulating evidence using next-generation sequencing (third tier testing) will increase the diagnostic yield even more over the next few years.” International Standard Cytogenomic Array Consortium

The International Standard Cytogenomic Array Consortium published a consensus statement in which it recommended offering CMA testing as the first-tier genetic test, in place of G-banded karyotype, for patients with unexplained DD/ID, ASD, or multiple congenital anomalies (MCA). "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, ASD, 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 fluorescent in situ hybridization (FISH) test such as subtelomeric FISH, and the yield is greater."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

REFERENCES


POLICY HISTORY

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<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>December 2011</td>
<td>New Policy</td>
<td>Policy updated with literature search, references 11,32,35,37,38 and 40 added, No change in policy statement</td>
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<tr>
<td>March 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 36, 40, 43 and 44 added. Policy statement added that NGS panel testing is considered investigational in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder. Title changed to include NGS.</td>
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<tr>
<td>June 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review through June 15, 2015. Policy statements changed that CMA may be considered medically necessary for apparently nonsyndromic developmental delay/intellectual disability, autism spectrum disorder, and multiple anomalies not specific to a well-delineated genetic syndrome. Reference 33 was added. Policy title updated.</td>
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Deborah M. Smith, MD, MPH