FEP Medical Policy Manual


Effective Policy Date: January 1, 2020

Original Policy Date: December 2011

Related Policies:
- 2.04.102 - Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders


Description

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

OBJECTIVE

The objective of this evidence review is to evaluate whether chromosomal microarray testing or gene panel testing with next-generation sequencing improves the net health outcome in individuals with developmental delay/intellectual disability, autism spectrum disorder, and/or congenital anomalies not specific to a well-delineated genetic syndrome.
POLICY STATEMENT

Chromosomal microarray analysis may be considered medically necessary as first-line testing in the initial evaluation (see Policy Guidelines) of individuals with any of the following:

- Apparent nonsyndromic developmental delay/intellectual disability,
- Autism spectrum disorder, or
- Multiple congenital anomalies not specific to a well-delineated genetic syndrome.

Chromosomal microarray is considered investigational for the evaluation of all other conditions of delayed development, including but not limited to idiopathic growth or language delay.

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

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

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

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

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

Genetics Nomenclature Update

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
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Variant | Change in the DNA sequence
---------|----------------------------------------------------------
Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

**Genetic Counseling**

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**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.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

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

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

**CMA Testing**

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

In January 2014, the Affymetrix CytoScan Dx Assay (Thermo Fisher Scientific) was cleared by the FDA through the de novo 510(k) process. The FDA's review of the CytoScan Dx Assay included an analytic evaluation of the test's ability to detect accurately numerous chromosomal variations of different types, sizes, and genome locations compared with several analytically validated test methods. The FDA found that the CytoScan Dx Assay could detect CNVs across the genome and adequately detect CNVs in regions of the genome associated with ID/DD. Reproducibility decreased with the CNV gain or loss size, particularly when less than approximately 400 kilobases (generally recommended as the lower reporting limit). As of July 2017, Affymetrix™ has 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). FDA product code: PFX.

FirstStepDX PLUS (Lineagen) uses Lineagen's custom-designed microarray platform manufactured by Affymetrix. As of July 2017, this microarray consists of a 2.8 million probe microarray for the detection of CNVs associated with neurodevelopmental disorders. The array includes probes that come standard on the Affymetrix CytoScan HD microarray, with an additional 88435 custom probes designed by Lineagen.

Ambry Genetics offers multiple tests (CMA and NGS) designed for diagnosing ASD and neurodevelopmental disorders. As of July 2017, the CMA offered by Ambry Genetics includes over 2.6 million probes for copy number and 750000 SNV probes. The expanded NGS panel for neurodevelopmental disorders includes assesses 196 genes.

LabCorp offers the Reveal SNP Microarray-Pediatric for individuals with nonsyndromic congenital anomalies, dysmorphic features, DD/ID, and/or ASD. The Reveal microarray has 2695 million probes as of July 2017.

**Next-Generation Sequencing**

A variety of commercial and academic laboratories offer 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.

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

Greenwood Genetics Center offers an NGS panel for syndromic autism that includes 83 genes.

**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. The relevant outcomes are test validity, changes in reproductive decision making, morbid events, and resource utilization. The available evidence supports test 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. Direct evidence of improved outcomes with CMA compared with karyotyping is also lacking. However, 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.

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Further, there is evidence of changes in reproductive decision making as a result of positive test results. The information derived from CMA testing can accomplish the following: it could end a long diagnostic odyssey, or reduce morbidity for certain conditions by initiating surveillance/management of associated comorbidities, or it could impact future reproductive decision making for parents. The evidence is sufficient to determine 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. The relevant outcomes are test validity, changes in reproductive decision making, morbid events, and resource utilization. The diagnostic yield associated with NGS panel testing in this patient population is not well-characterized. The testing yield and likelihood of an uncertain result are variable, based on the gene panel, gene tested, and patient population; additionally, there are 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

The American Academy of Pediatrics (2014) issued a clinical report on the optimal medical genetics evaluation of a child with developmental delays (DD) or intellectual disability (ID). Regarding chromosomal microarray (CMA) testing, this report stated "CMA now should be considered a first-tier diagnostic test in all children with [global] 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 Child and Adolescent Psychiatry

The American Academy of Child and Adolescent Psychiatry (2014) updated its guidelines on the assessment and treatment of children and adolescents with autism spectrum disorder (ASD). The Academy recommended that "all children with ASD should have a medical assessment, which typically includes physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis, and genetic testing, which may include G-banded karyotype, fragile X testing, or chromosomal microarray."

American Academy of Neurology and Child Neurology Society

The American Academy of Neurology and the Child Neurology Society (2011) updated their guidelines on the evaluation of unexplained DD and 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 ACMG (2010) published guidelines on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. CMA testing for copy number variants was recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

1. Multiple anomalies not specific to a well-delineated genetic syndrome
2. Apparently nonsyndromic DD/ID

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3. ASD.

Other ACMG guidelines have addressed the design and performance expectations for clinical microarrays and associated software, and for the interpretation and reporting of copy number variants, both intended for the postnatal setting. A 2013 update included recommendations on the validation of microarray methodologies for both prenatal and postnatal specimens.

The guideline revisions from ACMG (2013) stated that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of ASD is recommended, with the first tier including fragile X syndrome and CMA, and the second tier MECP2 and PTEN testing. The guidelines stated that:

"this approach will evolve with continued advancements in diagnostic testing and improved understanding of the ASD phenotype. Multiple additional conditions have been reported in association with an ASD phenotype, but none of these has been evaluated in a large prospective cohort. Therefore, a future third tier of evaluation is a distinct possibility. Further studies would be needed to elevate the evidence to the point of recommended testing. Alternatively, advances in technology may permit bundling of individual tests into an extended, more readily accessible, and less expensive platform. The accumulating evidence using next-generation sequencing (third-tier testing) will increase the diagnostic yield even more over the next few years."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

REFERENCES


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**POLICY HISTORY** - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<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>Replace 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>
</tr>
<tr>
<td>June 2014</td>
<td>Replace 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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<tr>
<td>December 2017</td>
<td>Replace</td>
<td>Policy updated with literature review through June 22, 2017; references 26-27 and 40 added; some references removed. Whole-exome sequencing is addressed separately in policy No. 2.04.102. The term “postnatal” removed from the policy statement. A second statement was added that chromosomal microarray is investigational for the evaluation of all other conditions of developmental delay.</td>
</tr>
<tr>
<td>December 2018</td>
<td>Replace</td>
<td>Policy updated with literature review through August 6, 2018; references 98-99 and 110 added. Policy statements unchanged.</td>
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<tr>
<td>December 2019</td>
<td>Replace</td>
<td>Policy updated with literature review through August 5, 2019; no references added. Policy statements unchanged.</td>
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