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FEP Medical Policy Manual

FEP 2.04.59 Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

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Related Policies:

2.04.102 - Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
2.04.116 - Invasive Prenatal (Fetal) Diagnostic Testing
2.04.122 - Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Description

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Chromosomal microarray (CMA) testing has been proposed for the 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, 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 guideline update from the 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Genetic Counseling

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.

BENEFIT APPLICATION

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

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.

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 next-generation sequencing 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 developmental delay/intellectual disability. 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™ contains 2.7 million markers for copy number, 750,000 SNVs, and 1.9 million non-polymorphic probes (Affymetrix was acquired by Thermo Fisher Scientific in 2016). FDA product code: PFX.

FirstStep^{Dx} 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 next-generation sequencing) 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 750,000 SNV probes. The expanded next-generation sequencing panel for neurodevelopmental disorders assesses 196 genes.

LabCorp offers the Reveal SNP Microarray-Pediatric for individuals with nonsyndromic congenital anomalies, dysmorphic features, developmental delay/intellectual disability, 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 next-generation sequencing panels designed for the evaluation of ASD, developmental delay/intellectual disability, and congenital anomalies, which vary in terms of the numbers of and specific genes tested.

Emory Genetics Laboratory offers a next-generation sequencing ASD panel of genes targeting genetic syndromes that include autism or autistic features. Greenwood Genetics Center offers a next-generation sequencing panel for syndromic autism that includes 83 genes. Fulgent Genetics offers a next-generation sequencing ASD panel that includes hundreds of genes.

RATIONALE

Summary of Evidence

For individuals who have developmental delay/intellectual disability, autism spectrum disorder, 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 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. 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, 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 an improvement in the net health outcome.

For individuals who have developmental delay/intellectual disability, autism spectrum disorder, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive next-generation sequencing panel testing, the evidence includes primarily case series. Relevant outcomes are test validity, changes in reproductive decision-making, morbid events, and resource utilization. The diagnostic yield associated with next-generation sequencing 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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 developmental delays or intellectual disability.[15,] Regarding chromosomal microarray (CMA) testing, this report stated: "CMA now should be considered a first-tier diagnostic test in all children with [global developmental delay/intellectual disability] 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."

In 2020, the AAP issued a clinical report on identifying infants and young children with developmental disorders through surveillance and screening.[109,] The report proposed a screening model that included performing a complete medical evaluation and stated that: "A child with suspected global developmental delay or intellectual disability should have laboratory testing done, including chromosomal microarray and fragile X testing [...] Further testing may be indicated when a diagnosis is not established with initial laboratory evaluation including whole exome sequencing and gene panels."

American Academy of Child and Adolescent Psychiatry

In 2014, the American Academy of Child and Adolescent Psychiatry updated its guidelines on the assessment and treatment of children and adolescents with autism spectrum disorder (ASD).[110,] 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

In 2011, the American Academy of Neurology and the Child Neurology Society updated their guidelines on the evaluation of unexplained developmental delay and intellectual disability with information on genetic and metabolic (biochemical) testing to accommodate advances in the field.[111,] The guidelines concluded that CMA testing has the highest diagnostic yield in children with developmental delay/intellectual disability, 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) (2010; reaffirmed 2020) published a clinical practice resource on array-based technologies and their clinical utilization for detecting chromosomal abnormalities.[112,113,] CMA testing for copy number variants was 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 disorder (ASD)

Other ACMG guidelines have addressed the design and performance expectations for clinical microarrays and associated software[8,114,] and for the interpretation and reporting of copy number variants,[11,] both intended for the postnatal setting.

A 2013 update included recommendations on the validation of microarray methodologies for both prenatal and postnatal specimens.[115,]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.[116,] 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.

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

Date	Action	Description
December 2011	New policy	
March 2013	Replace policy	Policy updated with literature search, references 11, 32, 35, 37, 38 and 40 added, No change in policy statement.
June 2014	Replace policy	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.
December 2015	Replace policy	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.
December 2016	Replace policy	Policy updated with literature review through July 10, 2016. References 6, 16, 21, 23-24, 33-35, and 40-42 added. Policy statements unchanged. Title changed to "Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies,.
December 2017	Replace policy	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.
December 2018	Replace policy	Policy updated with literature review through August 6, 2018; references 98-99 and 110 added. Policy statements unchanged.
December 2019	Replace policy	Policy updated with literature review through August 5, 2019; no references added. Policy statements unchanged.
December 2020	Replace policy	Policy updated with literature review through August 18, 2020; references added. Policy statements unchanged.
December 2021	Replace policy	Policy updated with literature review through August 20, 2021; no references added. Policy statements unchanged.
December 2022	Replace policy	Policy updated with literature review through August 22, 2022; references added. Policy statements unchanged.
December 2023	Replace policy	Policy updated with literature review through August 17, 2023; no references added. Policy statements unchanged.