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

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**Effective Date:** April 15, 2018

**Related Policies:**

2.04.122 Chromosomal Microarray Analysis for the Evaluation of Pregnancy Loss

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

#### Description

Chromosomal microarray (CMA) testing has been proposed for detection of genetic imbalances in infants or children with characteristics of developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), and/or congenital anomalies. CMA testing 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 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.

#### 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). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

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.

On August 11, 2017, the GenetiSure DX Postnatal Assay was cleared for marketing by FDA through Section 510(k) premarket notification. GenetiSure Dx Postnatal Assay is a qualitative assay intended for the postnatal detection of copy number variations (CNV) and copy-neutral loss of heterozygosity (cnLOH) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. GenetiSure Dx Postnatal Assay is intended for the detection of CNVs and cnLOH

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**Original Policy Date:** December 2011

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associated with developmental delay, intellectual disability, congenital anomalies or dysmorphic features. The assay is intended to be used on the SureScan Dx Microarray Scanner System and analyzed by CytoDx Software. FDA product code PFX

### 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
- 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 CMA testing as outlined in this policy is not intended for use in the prenatal period.

A 2013 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 chromosomal microarray (CMA) testing.

Recommendations from the 2010 American College of Medical Genetics guidelines (Manning et al 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 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. The nomenclature 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.

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**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

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

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).

### RATIONALE

#### Summary of Evidence

For individuals who have DD/ID, ASD, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive 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. Direct evidence of improved outcomes with CMA compared with karyotyping is 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; or reduce morbidity for certain conditions by initiating

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surveillance/management of associated comorbidities; or it could potentially 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 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 next-generation sequencing panel testing in this previously described 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; 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

In 2014, the American Academy of Pediatrics issued a clinical report on the optimal medical genetics evaluation of a child with or global developmental delays (GDD) or intellectual disability (ID).<sup>3</sup> Regarding chromosomal microarray (CMA) testing, this report stated

“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 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).<sup>42</sup> 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 global developmental delay (DD) and ID with information on genetic and metabolic (biochemical) testing to accommodate advances in the field.<sup>4</sup> 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 in 2010.<sup>43</sup> CMA testing for copy number variants (CNVs) was 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 DD/ID

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### C. ASD.

other ACMG guidelines have addressed the design and performance expectations for clinical microarrays and associated software<sup>8</sup> and for the interpretation and reporting of CNVs,<sup>16</sup> both intended for the postnatal setting. A 2013 update included recommendations on the validation of microarray methodologies for both prenatal and postnatal specimens.<sup>44</sup>

A 2013 guideline revisions from ACMG stated 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.<sup>45</sup> The guideline 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.”

### 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.”<sup>12</sup>

### 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.

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### POLICY HISTORY

Date	Action	Description
December 2011	New Policy	
March 2013	Update Policy	Policy updated with literature search, references 11,32,35,37,38 and 40 added, No change in policy statement
June 2014	Update 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.

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December 2015	Update 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	Update 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	Update 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.
March 2018	Administrative Update	Removed non-FEP policy title listed under the related policies section: 2.04.116 Invasive Prenatal (Fetal) Diagnostic Testing.

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