

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER, AND CONGENITAL ANOMALIES
POLICY NUMBER	MP 2.242

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

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I. POLICY

Chromosomal microarray analysis may be considered **medically necessary** in 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

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. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for this indication.

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. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for this indication.

POLICY GUIDELINES

Use of chromosomal microarray (CMA) testing as outlined in this policy is not intended for use in the prenatal period. For trio testing and rapid WES/WGS please see **MP 2.324 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders**.

A guideline update from American College of Medical Genetics (ACMG, Schaefer et al [2013]) states 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. CMA testing is recommended as first-tier evaluation in individuals who have the following:

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

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- “Apparently non-syndromic DD [developmental delay]/ID [intellectual disability].”
- “Autism spectrum disorders”

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.”

The International Standard Cytogenomic Array Consortium (ISCA, 2010) recommends offering CMA as a first-tier genetic test, in place of karyotype, for individuals with unexplained developmental delay/intellectual disability, autism spectrum disorders, or birth defects.

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.

Per the American Academy of Pediatrics, chromosomal microarray and fragile X testing are recommended for all children with ASD to predict prognosis. Chromosomal microarray will reveal genetic abnormalities in up to 42% of children with ASD. Fragile X testing is positive in less than 1% of patients with ASD, but it is important for genetic counseling. Targeted testing for disorders such as tuberous sclerosis and Rett syndrome is useful only if presentation suggests these disorders. Whole exome sequencing shows an abnormality in up to one-fifth of patients with ASD and can be considered if other testing is negative.

In 2020, the Pediatric Exome Sequencing/Genome Sequencing Guideline Work Group (Peds ES/GS GWG) was convened to develop an evidence-based guideline for the clinical use of ES/GS in patients with CA/DD/ID. They strongly recommended exome sequencing and genome sequencing as a first-tier or second-tier test (guided by clinical judgment and often clinician–patient/ family shared decision making after CMA or focused testing) for patients with one or more CAs prior to one year of age or for patients with DD/ID with onset prior to 18 years of age. This recommendation is echoed by the ACMG.

ACMG (2012) stated “Before initiating GS/ES, counseling should be performed by a medical geneticist or an affiliated genetic counselor and should include written documentation of consent from the patient.”

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

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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

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. counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-References:

MP 2.276 Genetic Testing for Pathogenic FMR1 Variants (Including Fragile X Syndrome)

MP 2.304 Autism Spectrum Disorders

MP 2.324 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

MP 7.009 Preimplantation Genetic Testing

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II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

III. DESCRIPTION/BACKGROUND

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Developmental Delay/Intellectual Disability

Developmental delay (DD), intellectual disability (ID), and congenital anomalies (CA) are among the most common indications for genetic referral in the pediatric population and comprise a heterogeneous group of conditions that can impact a child's physical, learning, or behavioral function. Identification of an underlying diagnosis for DD/ID/CA can lead to changes in management that will influence mortality, morbidity, and reduce the burden on patients and families searching for answers

Developmental delay is diagnosed in children 5 years or younger who show a significant delay in two or more developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living. DD can precede the development of intellectual disability (ID) as the child ages.

ID is manifest by significant limitations in intellectual functioning and adaptive behavior. It is diagnosed at or after age 5 (when intelligence testing is considered valid and reliable) but prior to age 18 and is lifelong. The *Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition (DSM-5)* defines ID as occurring during the developmental period and involving impairments of general mental abilities (e.g., IQ less than 70 or 75) that impact adaptive functioning in the conceptual, social, and practical domains. The causes of ID are extensive and include conditions that interfere with brain development and functioning. Among the known causes of ID, the majority are genetic abnormalities.

The national prevalence of DD and ID were estimated at 4.1% and 1.2%, respectively, in US children based on data from the 2009 to 2017 National Health Interview Survey. Both are influenced by genetic, environmental, infectious, and perinatal factors. Approximately 450 genes have been causally related to ID; most genes (~90%) are associated with syndromes. Inheritance of ID can be autosomal-dominant, recessive, or X-linked; and most nonsyndromic genes are located on the X chromosome. Prior to the advent of whole-exome and genome sequencing, Willemsen and Kleefstra (2014) concluded that 20% to 40% of ID cases could be attributed to a genetic variant. With the use of whole-genome sequencing, they estimated almost 60% of cases have an identifiable genetic etiology.

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Congenital anomalies are frequently present in children with DD and ID. In addition, a suspected etiology can often be established from history and physical examination (in skilled specialists as much as 20% to 40% of cases) without genetic testing. The recommended approach to evaluation in DD/ID begins with a 3-generation family history and physical (including neurologic) exam. Subsequent testing is used to confirm a suspected diagnosis (e.g., targeted fluorescent in situ hybridization [FISH] testing for DiGeorge or cri-du-chat syndromes). If no diagnosis is suspected, fragile X syndrome testing, metabolic testing for inborn errors of metabolism, and chromosomal microarray (CMA) testing (without karyotyping) are recommended-regardless of the presence or absence of dysmorphic features or congenital anomalies.

Autism Spectrum Disorder

DSM-5 defines autism spectrum disorder (ASD) as the presence of

- Persistent deficits in social communication and social interaction across multiple contexts,
- Restricted, repetitive patterns of behavior, interests, or activities,
- Symptoms in the early developmental period (typically recognized in the first 2 years of life), and
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

The estimated prevalence of ASD in US children based on data from the 2009 to 2017 National Health Interview Survey was 2.5%. ASD is 4 to 5 times more common in boys than girls, and white children are more often identified with ASD than black or Hispanic children. An accurate diagnosis can generally be made by age 2. The evaluation includes developmental screening and diagnostic evaluation (i.e., hearing, vision, neurologic, laboratory testing for metabolic disorders, and genetic testing).

A large body of evidence supports a genetic etiology in ASD. Twin studies estimate heritability between 60% and 90%. A family with an affected child has a 13% to 19% risk for recurrence in subsequent children. Based on Swedish genetic studies, Gaugler et al (2014) concluded that “the bulk of autism arises from genetic variation” (as opposed to environmental causes). Still, although genetic determinants can be heritable, most appear to arise de novo.

For these reasons, a child with ASD is often evaluated with genetic testing. Testing may be targeted when a child has a recognizable syndrome such as those shown in

Table 1. Alternatively, high-resolution cytogenetic analysis evaluating multiple genes-the focus of this evidence review-is used.

Table 1. Examples of Specific Genes Associated With Disorders That Include Autistic Behaviors

Gene (Syndrome)	Patient Selection	Yield, %	Reference
FMR1 (fragile X)	Unselected autism	3-10	Schaefer and Mendelsohn

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MECP2 (Rett)	Females with nonsyndromic autism, intellectual disability, and cerebral palsy	3-13	(2008) ²⁴
PTEN	Autism with macrocephaly	≤17	Butler et al (2005) ²⁵

Diagnostic Testing

Karyotyping and Fluorescent In Situ Hybridization

The goal of a cytogenetic evaluation is to identify chromosomal imbalances that cause a disorder. The most common imbalances are copy number variants (CNVs) or deletions and duplications of large segments of genomic material. CNVs are common in DD/ID and ASD but more often reflect the normal genetic variation. However, de novo CNVs are observed about four times more frequently in children with ASD than in normal individuals. Less frequently, other abnormalities such as balanced translocations (i.e., exchanges of equally sized DNA loci between chromosomes) may be pathogenic. For many well-described syndromes, the type and location of the associated chromosomal abnormality have been established by studying large patient samples. For others, few patients with similar abnormalities may have been evaluated to establish genotype-phenotype correlation. Finally, in some patients, cytogenetic analysis will discover chromosomal abnormalities that require study to determine their significance.

Prior to the advent of CMAs, the initial step in cytogenetic analysis was G-banded karyotyping, which evaluates all chromosomes. High-resolution G-banding can detect changes as small as 3 to 5 megabases in size, although standard G-banding evaluates more than ten megabases changes. In children with DD/ID, a review by Stankiewicz and Beaudet (2007) found G-banded karyotyping diagnostic in approximately 3% to 5% of cases. In ASD, high-resolution karyotyping appears to identify abnormalities in up to 5% of cases.

Chromosomal rearrangements in the gene-rich subtelomeric region are identified in approximately 4 to 6 percent of children with ID. Molecular screening using FISH of subtelomeric probes was used widely in the past to identify these abnormalities; however, CMA has replaced FISH as the test of choice, since the majority of diagnostic CMA arrays offer dense coverage of subtelomeric regions. FISH may still be substituted if array diagnosis is not available or if a specific telomeric disorder (e.g., DiGeorge syndrome, Cri-du-chat syndrome) is strongly suspected clinically.

In contrast, molecular cytogenetic techniques can detect small submicroscopic chromosomal alterations. Fluorescent in situ hybridization (FISH) a targeted approach, is used to identify specific chromosomal abnormalities associated with suspected diagnoses such as DiGeorge syndrome. Prior to CMAs, FISH was also used to screen the rearrangement-prone subtelomeric regions. Subtelomeric FISH was found to identify abnormalities in children with DD and ID, diagnostic in approximately 5% to 6% of those with negative karyotypes, but uncommonly in ASD.

Chromosomal Microarrays

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Two types of CMAs are considered here: array comparative genomic hybridization (aCGH) and single nucleotide variants (SNV) arrays. The aCGH approach uses DNA samples from a patient and a normal control. Each is labeled with distinct fluorescent dyes (red or green). The labeled samples are then mixed and hybridized to thousands of cloned or synthesized reference (normal) DNA fragments of known genomic locus immobilized on a glass slide (microarray) to conduct thousands of comparative reactions simultaneously. CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. If the patient sequence is missing part of the normal sequence (a deletion) or has the normal sequence plus additional genomic material within that genomic location (e.g., a duplication), the sequence imbalance is detected as a difference in fluorescence intensity (Korf and Rehm [2013] offer an illustrative graphic). For this reason, aCGH cannot detect balanced chromosomal translations (equal exchange of material between chromosomes) or sequence inversions (same sequence is present in reverse base pair order) because the fluorescence intensity would not change. A portion of the increased diagnostic yield from CMA over karyotyping comes from the discovery that chromosomal rearrangements that appear balanced (and therefore not pathogenic) by G-banded karyotype analysis are found to have small imbalances with greater resolution. It has been estimated that 40% of apparently balanced de novo or inherited translocations with abnormal phenotype are associated with cryptic deletion if analyzed by CMA testing.

Like aCGH, SNV arrays detect CNVs. In an SNV array, the two alleles for genes of interest are tagged with different fluorescent dyes. Comparative fluorescence intensity will be increased when there are duplications and diminished with deletions. The resolution provided by aCGH is higher than with SNV arrays. In addition, aCGH has better signal-to-background characteristics than SNV arrays. In contrast to aCGH, SNV arrays will also identify long stretches of DNA homozygosity, which may suggest uniparental disomy or consanguinity. Uniparental disomy occurs when a child inherits two copies of a chromosome from one parent and no copies from the other parent. Uniparental disomy can lead to syndromes such as Angelman and Prader-Willi.

Table 2 summarizes the cytogenetic tests used to evaluate children with DD/ID and autism. The table emphasizes the large difference in resolution between karyotyping and CMA.

Table 2. Resolution and Analysis Comparison of FISH, Karyotyping, and CMA Analysis

Test	Resolution in Kilobases ^a	Analysis
Karyotyping	3000-5000 kb	Genome-wide
CMA	≈50 kb	Genome-wide
FISH	≈500 to 1000 kb (depending on probe)	Targeted

CMA: chromosomal microarray; FISH: fluorescent in situ hybridization; kb: kilobases.

^a One kb = 1000 bases, 1000 kb = 1 Mb.

Microarrays may be prepared by the laboratory using the technology or, more commonly, by commercial manufacturers, and sold to laboratories that must qualify and validate the product for use in their assay, in conjunction with computerized software for interpretation. The

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proliferation of laboratory-developed and commercially available platforms prompted the American College of Medical Genetics to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting.

Next-Generation Sequencing

Next-generation sequencing (NGS) has been proposed to detect single-gene causes of autism and possibly identify a syndrome that involves autism in patients with normal array-based testing. NGS involves the sequencing of millions of fragments of genetic material in a massively parallel fashion. NGS can be performed on segments of genetic material of various sizes—from the entire genome (whole-genome sequencing) to small subsets of genes (targeted sequencing). NGS allows the detection of SNVs, CNVs, insertions, and deletions. With higher resolution comes higher likelihood of detection of variants of uncertain significance.

Exome and Genome Sequencing

Exome sequencing utilizes DNA-enrichment methods and massively parallel nucleotide sequencing to identify disease-associated variants throughout the human genome. Exome sequencing is limited to the DNA sequence of coding regions (exons) and flanking intronic regions of the genome, which is estimated to contain 85% of heritable disease-causing variants. Results of testing with ES include known pathogenic variants definitely associated with disease or a variant of uncertain significance. Due to the falling costs of sequencing and its high diagnostic yield, WES is rapidly becoming a clinical tool for the evaluation of ID, especially at specialty centers. Exome sequencing after standard testing increased the diagnostic yield at an additional cost compared to standard testing alone. However, using ES as a first- or second-tier test (e.g., after CMA or targeted testing) yielded more diagnoses at a lower cost than using ES only after extensive standard testing (e.g., large sequencing panels and/or multiple testing approaches) or using standard testing alone. With the anticipated further declines in cost, early use of genome-wide sequencing should continue to enable more timely diagnosis for patients with unexplained DD or multiple Cas.

Whole genome sequencing is costlier than more limited sequencing, because the whole genome is equivalent to approximately 3.3×10^9 bases (3.3 gigabases [Gb]). Whole genome sequencing may become preferable to exome sequencing as cost decreases and more information about the role of non-coding DNA in human disease becomes available. Further, whole genome sequencing can be used to detect deletions and duplications typically detected only by array comparative genomic hybridization (aCGH) and thus is an opportunity to reduce the need for other supplemental testing. One of the most common medical indications for whole genome sequencing or whole exome sequencing is evaluation of severe intellectual disability or developmental delay believed to have a genetic etiology in a child with a negative initial evaluation.

The value of genetic counseling in exome and genome sequencing is well-established. Creating reasonable expectations, establishing an understanding of the value and limitations of testing, creating awareness of the potential harms, and allowing the family to make informed choices is a mainstay of informed consent for ES/GS. These visits should also be commensurate with the

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time spent as part of the clinical process including reimbursement for this type of counseling. Post-test counseling extends this benefit once the results are available regardless of the diagnostic yield. Elements of counseling should include a three-generation family pedigree; discussion of pathogenic/likely pathogenic results, benign results, and variants of uncertain significance; detection of misattributed paternity or consanguinity, and secondary findings unrelated to the reason for testing.

Genetic Associations with DD/ID and ASD

For common phenotypes and syndromes, the pathogenicity of CNVs may be supported by considerable evidence; for uncommon phenotypes and uncommon CNVs determining pathogenicity requires a systematic evaluation that includes parental studies, examining databases for reported associations, and considering the molecular consequences of the identified variant. Parental studies (e.g., “trio” testing of affected child, father, and mother) can identify an inherited CNV from an unaffected parent and therefore considered benign. A variety of databases index the clinical implications of CNVs and their associations with a particular phenotype. CNVs are continuously cataloged and, with growth in CMA testing and improved resolution, databases have become increasingly extensive (e.g., DECIPHER, ClinVar). For uncommon CNVs, in addition to reports of CNV-phenotype associations, the location and size of the CNV can offer clues to pathogenicity; larger CNVs are more often pathogenic and the role of affected genes in brain circuitry and effect of CNV on gene expression can implicate pathogenicity. Although uncommon, an observed phenotype can result from unmasking a mutated recessive allele on the unaffected (non-CNV) chromosome. Other considerations when determining pathogenicity include CNV dosage, X linkage, number of reports in the literature of an association between CNV and phenotype, and findings in “normal” individuals.

The American College of Medical Genetics has published guidelines for evaluating, interpreting, and reporting pathogenicity reflecting these principles. The recommended categories of clinical significance for reporting are pathogenic, uncertain clinical significance (likely pathogenic, likely benign, or no subclassification), or benign. The International Standards for Cytogenomic Arrays Consortium more recently proposed “an evidence-based approach to guide the development of content on chromosomal microarrays and to support interpretation of clinically significant copy number variation.” The proposal defined levels of evidence describe how well or how poorly detected variants or CNVs correlate with phenotype.

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.

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In 2010, 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 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 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 four hundred kilobases (generally recommended as the lower reporting limit). As of July 2017, Affymetrix™ has reported 2.7 million markers for copy number, 750,000 SNVs and 1.9 million 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 88,435 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 750,000 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 eighty-three genes. Fulgent Genetics offers a next-generation sequencing ASD panel that includes 121 genes.

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IV. RATIONALE

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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 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 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 exome and genome sequencing, the growing body of literature provides justification for a strong recommendation based desirable effects and limited harms. The evidence is sufficient to determine that the technology results in 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 diagnostic yield associated with next-generation sequencing panel testing in this patient population is not well-characterized. The testing yield and likelihood of uncertain results are 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.

V. DEFINITIONS

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ANALYTIC VALIDITY of a genetic test defines its ability to accurately and reliably measure the genotype of interest.

CHROMOSOME is one of the threadlike “packages” of genes and other DNA in the nucleus of a cell.

CLINICAL VALIDITY of a genetic test defines its ability to detect or predict the associated disorder (phenotype).

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COMPARATIVE GENOMIC HYBRIDIZATION (CGH) also referred to as chromosomal microarray analysis (CMA), and array CGH (aCGH) is a technique which produces a map of DNA sequence copy number as a function of chromosomal location throughout the entire genetic genome, and allows the detection of genetic deletions, duplications, and amplifications.

DNA a large nucleic acid molecule, found principally in the chromosomes of the nucleus of a cell, that is the carrier of genetic information.

FIRST-DEGREE RELATIVE refers to a parent, sibling, or child.

GENE is the basic unit of heredity, made of DNA, the code for a specific protein.

GENOTYPE is the specific genetic makeup of an individual, usually in the form of DNA.

KARYOTYPE is the chromosomal complement of an individual, including the number of chromosomes and any abnormalities.

MICROARRAY is a tool for analyzing gene expression that consists of a small membrane or glass slide containing samples of many genes arranged in a regular pattern. Each spot on an array is associated with a particular gene. Each color in an array represents either healthy (control) or diseased (sample) tissue. Depending on the type of array used, the location and intensity of a color will indicate whether the gene, or mutation, is present in either the control and/or sample DNA. It will also provide an estimate of the expression level of the gene(s) in the sample and control DNA.

MITOCHONDRIA are intracellular organelles that are responsible for energy production and cellular respiration.

MITOCHONDRIAL DISEASE refers to one of hundreds of congenital illnesses that result from mutations in mitochondrial DNA. As a result, the mitochondria are unable to completely burn food and oxygen in order to generate energy.

MUTATION is a permanent structural alteration in DNA.

PHENOTYPE is the physical characteristics of an organism or the presence of a disease that may or may not be genetic.

RNA is a chemical similar to a single strand of DNA

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and

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exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered.

Procedure Codes								
0156U	0170U							

Covered when medically necessary:

Procedure Codes								
S3870	0209U	0318U	81228	81229	81349	81470	81471	

ICD-10-CM Diagnosis Codes	Description
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F73	Profound intellectual disabilities
F78	Other intellectual disabilities
F78.A1	SYNGAP1-related intellectual disability
F78.A9	Other genetic related intellectual disability
F80.0	Phonological disorder
F82	Specific developmental disorder of motor function
F84.0	Autistic disorder
F84.2	Rett's syndrome
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F88	Other disorders of psychological development
Q89.7	Multiple congenital malformations, not elsewhere classified
QA0	Neurodevelopmental disorders related to specific genetic pathogenic variants

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ICD-10-CM Diagnosis Codes	Description
QA0.0	Neurodevelopmental disorders related to pathogenic variants in specific genes
QA0.01	Neurodevelopmental disorders related to pathogenic variants in certain specific genes
QA0.010	Neurodevelopmental disorders, related to pathogenic variants in ion channel genes
QA0.013	Neurodevelopmental disorders, related to pathogenic variants in other transporter and solute carrier genes
QA0.014	Neurodevelopmental disorders, related to pathogenic variants in synapse related genes
QA0.015	Neurodevelopmental disorders, related to genes associated with transcription and gene expression

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IX. POLICY HISTORY

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MP 2.242	01/01/2020 Administrative Update. New code 0156U added.
	02/26/2020 Consensus Review. No changes to policy statement. Coding reviewed. New code 0170U added as investigational, effective 04/01/2020.
	10/01/2020 Administrative Update. New code 0209U added, effective 10/01/2020.
	09/07/2021 Administrative Update. New codes F78.A1 and F78.A0 added. Effective 10/01/2021
	10/04/2021 Consensus Review. No change to policy statement. Description/background and references updated. Coding section revision: 0156U moved from medically necessary to investigational.
	03/11/2022 Administrative Update. New code 0318U added as conditionally covered; effective 04/01/2022.
	08/30/2022 Minor Review. Exome and genome sequencing now MN. Literature review and update. Societal recommendations added to policy

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER, AND CONGENITAL ANOMALIES
POLICY NUMBER	MP 2.242

	guidelines. Supporting information added to background. Added 2.324 to cross ref. Ref update. 81349 added, 0209U moved from INV to MN.
	07/26/2023 Minor Review. Added criteria for standard whole exome and genome sequencing to including genetic counseling and clarify appropriate timing of testing. Updates to background, references. CPT codes added to include WES/WGS codes: 0212U, 0214U, 0265U, 0267U, 81415, 81417, 81425, 81427.
	01/19/2024 Administrative Update. Clinical benefit added.
	10/07/2024 Consensus Review. No change to policy stance. Updated references.
	07/07/2025 Minor review. Removed criteria regarding whole exome and whole genome sequencing as this is addressed in MP 2.324 . Codes 0267U, 0212U, 0214U, 0265U, 81415, 81417, 81425, and 81427 removed from policy; remain on MP 2.324 .
	09/02/2025 Administrative Update. New ICD10 codes added effective 10/1/25
	10/09/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/05/2026 Retirement Review. EviCore delegation.

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