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## Genetic Testing, Including Chromosomal Microarray Analysis and Next-Generation Sequencing Panels, for the Evaluation of Developmental Delay/Intellectual Disability, Autism Spectrum Disorder and/or Congenital Anomalies Corporate Medical Policy

File Name: Genetic Testing, Including Chromosomal Microarray Analysis and Next Generation Sequencing Panels, for the Evaluation of Developmental Delay/Intellectual Disability, Autism Spectrum Disorder and/or Congenital Anomalies

File Code: 2.04.VT59

Origination: 07/2011

Last Review: 12//2024

Next Review: 12/2025

Effective Date: 03/01/2025

### Description/Summary

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

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 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 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 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.

## Policy

### Coding Information

[Click the links below for attachments, coding tables & instructions.](#)

[Attachment I- CPT® & HCPCS Code List & Instructions](#)

### When a service may be considered medically necessary

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

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

### When a service is considered investigational

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

This policy is aligned with the Blue Cross and Blue Shield Association policy MPRM 2.04.59. Use of chromosomal microarray (CMA) testing as outlined in this policy is not intended for use in the prenatal period.

## 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.

## Reference Resources

1. Blue Cross and Blue Shield Medical Policy. MPRM 2.04.59. Last reviewed 11/2023. Accessed 11/2024.

## Document Precedence

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract language, the member's contract language takes precedence.

## Audit Information

BCBSVT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.

## Administrative and Contractual Guidance

### Benefit Determination Guidance

Prior approval is required and benefits are subject to all terms, limitations and conditions of the subscriber contract.

NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member's health plan.

Federal Employee Program (FEP) members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure.

Coverage varies according to the member’s group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services Only (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member’s employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

### Policy Implementation/Update information

07/2011	New policy
09/2012	Minor format changes made. Added file code name. Added “Document Precedence” section. Updated “Related Policies” section to reflect Early Childhood Developmental Disorders medical policy (fka: Autism Spectrum Disorder, Coverage of Services). Audit Information section added.
08/2015	Adopted BCBSA policy# 2.04.59
10/2018	Policy reviewed. Policy statements updated under Investigational section. Removed ICD-10-CM table. Codes 81243 & 81244 require Prior Approval.
11/2020	Policy reviewed. No changes to policy statements made. Reference dates updated.
01/2021	Adaptive Maintenance effective 01/01/21: Added code 0234U requires prior approval. Codes added from current investigational policy to coding table 0156U effective 01/01/2020, 0170U effective 04/01/2020, 0209U effective 10/01/2020.
10/2021	Adaptive Maintenance Effective 10/01/2021: Added code 0263U as investigational.
12/2021	Reviewed Policy no changes to policy statements. Adaptive Maintenance Effective 01/01/2022: Code 81349 added as requiring prior approval. Codes 81228 & 81229 descriptors revised.
11/2022	Policy reviewed. No changes to policy statement. Clarified CMA testing as outlined in the medical policy as indicated postnatal testing. Update reference.
11/2023	Policy reviewed. Updated reference. Added information re: next generation sequencing in description/summary. No change to policy statement. Revised codes 81243 & 81244. Descriptor revised effective 01/01/2024.
12/2024	Policy reviewed. No change to policy statement.

### Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).

Approved by BCBSVT Medical Director

Tom Weigel, MD, MBA  
Vice President and Chief Medical Officer

Tammaji P. Kulkarni, MD  
Senior Medical Director

Attachment I  
CPT® & HCPCS Code List & Instructions

Code Type	Number	Description	Policy Instructions
<b>The following codes are considered as medically necessary when applicable criteria have been met.</b>			
CPT®	81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis	Prior Approval Required
CPT®	81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis	Prior Approval Required
CPT®	81243	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles	Prior Approval Required
CPT®	81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)	Prior Approval Required
CPT®	81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities	Prior Approval Required

Code Type	Number	Description	Policy Instructions
CPT®	81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2	Prior Approval Required
CPT®	81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2	Prior Approval Required
CPT®	0156U	Copy number (eg, intellectual disability, dysmorphism), sequence analysis	Investigational
CPT®	0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis	Investigational
CPT®	0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities	Investigational
CPT®	0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions	Prior Approval Required

Code Type	Number	Description	Policy Instructions
CPT®	0263U	Neurology (autism spectrum disorder [ASD]), quantitative measurements of 16 central carbon metabolites (ie, aketoglutarate, alanine, lactate, phenylalanine, pyruvate, succinate, carnitine, citrate, fumarate, hypoxanthine, inosine, malate, S-sulfocysteine, taurine, urate, and xanthine), liquid chromatography tandem mass spectrometry (LC-MS/MS), plasma, algorithmic analysis with result reported as negative or positive (with metabolic subtypes of ASD)	Investigational
HCPCS	S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability	Prior Approval Required