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: UM.GEN.01
Origination: 07/2011
Last Review: 11/2018
Next Review: 11/2019
Effective Date: 07/01/2019

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.

**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 postnatal evaluation of individuals with any of the following:

- Apparently non-syndromic developmental delay/intellectual disability
- Autism spectrum disorder
- 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.

**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.

**Rationale**

BCBS Association MPRM 2.04.59: This evidence review was created in January 2010 and
has been updated regularly with a search of the MEDLINE database. The most recent literature update was performed through August 6, 2018.

This review has been informed by a TEC Special Report (2009) on array comparative genomic hybridization (aCGH) and a TEC Special Report (2015) on chromosomal microarray (CMA) testing for the genetic evaluation of patients with global developmental delay (DD), intellectual disability (ID), and autism spectrum disorder (ASD). Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition. The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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 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 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 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 the effects of the technology on health outcomes.

Reference Resources

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

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<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>7/2011</td>
<td>New policy</td>
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<tr>
<td>9/2012</td>
<td>Minor format changes made. Added file code name</td>
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<td></td>
<td>Added “Document”</td>
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08/2015 Adopted BCBSA policy# 2.04.59


Approved by BCBSVT Medical Directors Date Approved

Joshua Plavin, MD, MBA
Chief Medical Officer

Attachment I
CPT® & HCPCS Code List & Instructions

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Number</th>
<th>Description</th>
<th>Policy Instructions</th>
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<tbody>
<tr>
<td>CPT®</td>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
<td>Prior Approval Required</td>
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<tr>
<td>CPT®</td>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
<td>Prior Approval Required</td>
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<td>CPT®</td>
<td>81243</td>
<td>FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles</td>
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<td>CPT®</td>
<td>81244</td>
<td>FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and methylation status)</td>
<td>Prior Approval Required</td>
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<tr>
<td>CPT®</td>
<td>81470</td>
<td>X-linked intellectual disability (XLID) (eg,</td>
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<tr>
<td>CPT&lt;sup&gt;®&lt;/sup&gt;</td>
<td>81471</td>
<td>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</td>
<td>Prior Approval Required</td>
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<tr>
<td>HCPCS</td>
<td>S3870</td>
<td>Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability</td>
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