Genetic Testing for Rett Syndrome

Description

Rett syndrome (RTT), a neurodevelopmental disorder, is usually caused by pathogenic variants in the methyl-CpG-binding protein 2 (MECP2) gene. Genetic testing is available to determine whether a pathogenic variant exists in RTT-associated genes (e.g., MECP2, FOXG1, or CDKL5) in a patient with clinical features of RTT or a patient's family member.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for Rett (RTT)-associated genes improves the net health outcome in individuals with signs and/or symptoms of RTT. This review does not encompass those who are asymptomatic sisters of a child with RTT with a known pathogenic variant, or women with a child with RTT with a known pathogenic variant who are considering further childbearing.

POLICY STATEMENT

Genetic testing for Rett syndrome-associated genes (e.g., MECP2, FOXG1, or CDKL5) may be considered medically necessary to establish a genetic diagnosis of Rett syndrome in a child with developmental delay and signs/symptoms of Rett syndrome, when a definitive diagnosis cannot be made without genetic testing.
POLICY GUIDELINES

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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
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<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
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<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
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<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
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<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
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<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
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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.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
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.

**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).

**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. Genetic testing for Rett syndrome is available under the auspices of the 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 has chosen not to require any regulatory review of this test.

**RATIONALE**

**Summary of Evidence**

For individuals who have signs and/or symptoms of RTT who receive genetic testing for RTT-associated genes, the evidence includes case series and prospective cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, health status measures, and quality of life. MECP2 variants are found in most patients with RTT, particularly in those who present with classic clinical features of RTT. The diagnostic accuracy of genetic testing for RTT cannot be determined with absolute certainty given variable clinical presentations of typical vs atypical RTT, but testing appears to have high sensitivity and specificity. Genetic testing has clinical utility when signs and symptoms of RTT are present to establish a specific genetic diagnosis. Identification of a specific class or type of pathogenic variant may alter some aspects of management and may eliminate or necessitate surveillance for different clinical manifestations of the disease. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

**American Academy of Neurology and Child Neurology Society**


**American Academy of Pediatrics**

A 2007 policy statement25 from the American Academy of Pediatrics, reaffirmed in 2014,26 recommended MECP2 testing to confirm a diagnosis of suspected Rett syndrome (RTT), especially when the diagnosis was unclear from symptoms alone.

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Neither the American Academy of Neurology nor the American Academy of Pediatrics has provided recommendations on when to use CDKL5 or FOXG1 testing.

**RettSearch Consortium**

In 2010, RettSearch, a consortium of international clinical RTT specialists, suggested that patients who are negative for MECP2 variants and have a strong clinical diagnosis of RTT should be considered for further screening for the CDKL5 gene if there are early-onset seizures, or for the FOXG1 gene if there are congenital features (eg, severe postnatal microcephaly).³

**American College of Medical Genetics and Genomics**

The American College of Medical Genetics and Genomics (2013) revised its evidence-based guidelines for clinical genetics evaluation of autism spectrum disorders.² Testing for MECP2 genetic variants was recommended as part of the diagnostic workup of females who present with an autistic phenotype. Routine MECP2 testing in males with autism spectrum disorders was not recommended.

**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.

**REFERENCES**


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

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<tr>
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<th>Action</th>
<th>Description</th>
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<tr>
<td>December 2012</td>
<td>New policy</td>
<td>Policy updated with literature search, references 3-6, 10, and 11 added. Policy statements unchanged</td>
</tr>
<tr>
<td>December 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature search, references 3-6, 10, and 11 added. Policy statements unchanged</td>
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<td>Replace policy</td>
<td>Policy updated with literature search adding references 6, 8-11, 17, and 19 -22. No change to policy statements</td>
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<tr>
<td>June 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 23, 2017; references 12-14, and 21-23. The policy is revised with updated genetics nomenclature. “Mutations” changed to “variants” in policy statements. Policy statements updated to define “genetic testing for Rett-syndrome associated genes (eg, MECP2, FOXG1 or CDKL5)”. Removed “female” requirement of child for testing; Added two new medical necessity statements for “targeted genetic testing for a known familial variant” in a sister of a child with Rett syndrome or a female with a child with Rett syndrome</td>
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<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 5, 2018; references 23-24 added. Policy statements for “targeted genetic testing for a known familial variant” in a sister of a child with Rett syndrome or a female with a child with Rett syndrome removed as not in the scope of review of this policy due to current FEP benefit limitation for testing of asymptomatic individuals.</td>
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<tr>
<td>September 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 4, 2019; no references added. Policy statements unchanged.</td>
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