FEP 2.04.81 Genetic Testing for Rett Syndrome

**Effective Date:** July 15, 2017  
**Related Policies:** None

---

**Genetic Testing for Rett Syndrome**

**Description**

Rett syndrome (RTT) is a severe neurodevelopmental disorder primarily affecting girls with an incidence of 1:10,000 female births, making it one of the most common genetic causes of intellectual disability in girls.1 RTT is characterized by apparent normal development for the first 6 to 18 months of life, followed by the loss of intellectual functioning, loss of acquired fine and gross motor skills and the ability to engage in social interaction. Purposeful use of the hands is replaced by repetitive stereotyped hand movements, sometimes described as hand-wringing. Other clinical manifestations include seizures, disturbed breathing patterns with hyperventilation and periodic apnea, scoliosis, growth retardation and gait apraxia.

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

**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. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**POLICY STATEMENT**

Genetic testing for Rett syndrome-associated genes (eg, 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.

Targeted genetic testing for a known familial Rett syndrome-associated variant may be considered medically necessary to determine carrier status of a mother or a sister of an individual with Rett syndrome.

All other indications for genetic testing for Rett syndrome-associated genes (eg, MECP2, FOXG1, or CDKL5), including carrier testing (preconception or prenatal), and testing of asymptomatic family members to determine future risk of disease, are considered investigational.
FEP 2.04.81 Genetic Testing for Rett Syndrome

POLICY GUIDELINES

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 signs and/or symptoms of Rett syndrome (RTT), the evidence for genetic testing for Rett-syndrome-associated genes 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 those who present with classical clinical features of RTT. The diagnostic accuracy of genetic testing for RTT cannot be determined with absolute certainty given variable clinical presentations of typical versus atypical RTT, but testing appears to have high sensitivity and specificity. Genetic testing has clinical utility when signs and symptoms of Rett syndrome 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 disease. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic sisters of a child with RTT with a known pathogenic variant, the evidence for targeted familial variant testing includes case series and prospective cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, changes in reproductive decision making, symptoms, and symptoms. Targeted familial variant testing of asymptomatic sisters can eliminate or necessitate surveillance given the variability of clinical presentation in girls due to X-chromosome inactivation and clinical severity based on the type of pathogenic variant present. In reproductive-age sisters, determination of carrier status can eliminate or necessitate prenatal testing and inform reproductive decision making. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are women with a child with RTT and who are considering future childbearing, the evidence for targeted genetic testing for a familial Rett syndrome-associated variant includes cases series and prospective cohort studies. Relevant outcomes are test accuracy and validity, other test performance...
measures, and changes in reproductive decision making. Targeted familial variant testing of a woman with a child with RTT to determine carrier status may inform prenatal testing and reproductive decision making. In the rare situation where the mother carries a pathogenic variant, all future offspring have a 50% of being affected with males typically presenting with more severe disease. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
American Academy of Pediatrics
A 2007 policy statement from the American Academy of Pediatrics (AAP; reaffirmed in 201026) recommended MECP2 testing to confirm a diagnosis of suspected RTT, especially when the diagnosis was unclear from symptoms alone.

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.

REFERENCES
FEP 2.04.81 Genetic Testing for Rett Syndrome


POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2012</td>
<td>New Policy</td>
<td>Policy updated with literature search, references 3-6, 10, 11 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>December 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search adding references 6, 8-11, 17, and 19-22. No change to policy statements.</td>
</tr>
<tr>
<td>December 2014</td>
<td>Update 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. &quot;Mutations&quot; changed to &quot;variants&quot; in policy statements. Policy rewritten with new PICOs for Indications 2 and 3 to limit populations to sisters of child with Rett syndrome (Indication 2) or females with a child with Rett syndrome (Indication 3) with the intervention revised to &quot;targeted genetic testing for a known familial variant.&quot; Policy statements updated to define &quot;genetic testing for Rett-syndrome associated genes (eg, MECP2, FOXG1 or CDKL5)&quot;; Removed &quot;female&quot; requirement of child for testing; Added two new medical necessity statements for &quot;targeted genetic testing for a known familial variant&quot; in a sister of a child with Rett syndrome or a female with a child with Rett syndrome.</td>
</tr>
<tr>
<td>June 2017</td>
<td>Revised 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. &quot;Mutations&quot; changed to &quot;variants&quot; in policy statements. Policy rewritten with new PICOs for Indications 2 and 3 to limit populations to sisters of child with Rett syndrome (Indication 2) or females with a child with Rett syndrome (Indication 3) with the intervention revised to &quot;targeted genetic testing for a known familial variant.&quot; Policy statements updated to define &quot;genetic testing for Rett-syndrome associated genes (eg, MECP2, FOXG1 or CDKL5)&quot;; Removed &quot;female&quot; requirement of child for testing; Added two new medical necessity statements for &quot;targeted genetic testing for a known familial variant&quot; in a sister of a child with Rett syndrome or a female with a child with Rett syndrome.</td>
</tr>
</tbody>
</table>

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.