Medical Policy
Genetic Testing for Rett Syndrome

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Policy Number: 803
BCBSA Reference Number: 2.04.81
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)
MECP2 Genetic Testing Coding and Billing Guidelines (M00066, V5)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Mutation testing for Rett syndrome may be considered **MEDICALLY NECESSARY** to confirm a diagnosis of Rett syndrome in a female child with developmental delay and signs/symptoms of Rett syndrome, when a definitive diagnosis cannot be made without genetic testing.

All other indications for mutation testing for Rett syndrome, including carrier testing (preconception or prenatal), and testing of asymptomatic family members to determine future risk of disease, are considered **INVESTIGATIONAL**.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at [https://www.cms.gov](https://www.cms.gov).
Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
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</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>This is not a covered service.</td>
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</table>

CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81302</td>
<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81303</td>
<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81304</td>
<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
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<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
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Description
Rett Syndrome
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.\(^1\) Other clinical manifestations include seizures, disturbed
breathing patterns with hyperventilation and periodic apnea, scoliosis, growth retardation and gait apraxia.²

There is wide variability in the rate of progression and severity of the disease. In addition to the classical form of RTT, there are a number of recognized atypical variants. Variants of RTT may appear with a severe or a milder form. The severe variant has no normal developmental period; individuals with a milder phenotype experience less dramatic regression and milder expression of the characteristics of classical RTT.

The diagnosis of RTT remains a clinical one, using diagnostic clinical criteria that have been established for the diagnosis of classic and variant RTT.¹⁻³

Treatment of RTT
Currently, there are no specific treatments that halt or reverse the progression of the disease, and there are no known medical interventions that will change the outcome of patients with RTT. Management is mainly symptomatic and individualized, focusing on optimizing each patient’s abilities.¹ A multidisciplinary approach is usually applied, with specialist input from dietitians, physiotherapists, occupational therapists, speech therapists and music therapists. Regular monitoring for scoliosis (seen in ≈87% of patients by age 25 years) and possible heart abnormalities may be recommended. Spasticity can have a major impact on mobility; physical therapy and hydrotherapy may prolong mobility. Occupational therapy can help children develop communication strategies and skills needed for performing self-directed activities (eg, dressing, feeding, practicing arts and crafts).

Pharmacologic approaches to managing problems associated with RTT include melatonin for sleep disturbances and several agents for the control of breathing disturbances, seizures, and stereotypic movements. RTT patients have an increased risk of life-threatening arrhythmias associated with a prolonged QT interval, and avoidance of a number of drugs is recommended, including prokinetic agents, antipsychotics, tricyclic antidepressants, antiarrhythmics, anesthetic agents and certain antibiotics. In a mouse model of RTT, genetic manipulation of mutated MECP2 has demonstrated reversibility of the genetic defect.⁴⁻⁵

Genetics of RTT
RTT is an X-linked dominant genetic disorder. Mutations in MECP2, which is thought to control expression of several genes including some involved in brain development, were first reported in 1999. Subsequent screening has shown that over 80% of patients with classical RTT have pathogenic mutations in the MECP2 gene. More than 200 mutations in MECP2 have been associated with RTT.⁶ However, 8 of the most commonly occurring missense and nonsense mutations account for almost 70% of all cases; small C-terminal deletions account for approximately 10%; and large deletions, 8% to 10%.⁷ MECP2 mutation type is associated with disease severity.⁸ Whole duplications of the MECP2 gene have been associated with severe X-linked intellectual disability with progressive spasticity, no or poor speech acquisition, and acquired microcephaly. Additionally, the pattern of X-chromosome inactivation influences the severity of the clinical disease in females.⁹⁻¹⁰

Because the spectrum of clinical phenotypes is broad, to facilitate genotype-phenotype correlation analyses, the International Rett Syndrome Association has established a locus-specific MECP2 variation database (RettBASE) and a phenotype database (InterRett).

Approximately 99.5% of cases of RTT are sporadic, resulting from a de novo mutation, which arise almost exclusively on the paternally derived X chromosome. The remaining 0.5% of cases are familial and usually explained by germline mosaicism or favorably skewed X-chromosome inactivation in the carrier mother that results in her being unaffected or only slightly affected (mild intellectual disability). In the case of a carrier mother, the recurrence risk of RTT is 50%. If a mutation is not identified in leukocytes of the mother, the risk to a sibling of the proband is below 0.5% (because germline mosaicism in either parent cannot be excluded).
Identification of a mutation in MECP2 does not necessarily equate to a diagnosis of RTT. Rare cases of MECP2 mutations also have been reported in other clinical phenotypes, including individuals with an Angelman-like picture, nonsyndromic X-linked intellectual disability, PPM-X syndrome (an X-linked genetic disorder characterized by psychotic disorders [most commonly bipolar disorder], parkinsonism, and intellectual disability), autism, and neonatal encephalopathy.1,6,11

A proportion of patients with a clinical diagnosis of RTT do not appear to have mutations in the MECP2 gene. Two other genes, CDKL5 and FOXG1, have been shown to be associated with atypical variants.

Summary
Rett syndrome (RTT), a neurodevelopmental disorder, is usually caused by mutations in the MECP2 (methyl-CpG-binding protein 2) gene. Genetic testing is available to determine whether a pathogenic mutation exists in a patient with clinical features of RTT, or in a patient's family member.

The evidence for genetic testing to confirm a diagnosis in patients who have signs and/or symptoms of RTT includes case series. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, health status measures, and quality of life. MECP2 mutations are found in most patients with RTT, particularly those who present with classical clinical features of RTT. The diagnostic accuracy of mutation testing for RTT cannot be determined with absolute certainty given the lack of a true criterion standard for RTT diagnosis, but testing appears to have high sensitivity and specificity. Diagnostic testing has clinical utility when signs and symptoms of Rett syndrome are present, but a definitive diagnosis cannot be made without genetic testing. Confirming a diagnosis may alter some aspects of management and may eliminate the need for further diagnostic workup. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing of asymptomatic family members who have a family member with RTT to determine future risk of disease includes case series. Relevant outcomes are test accuracy and validity, other test performance measures, changes in reproductive decision making, symptoms, and symptoms. Testing of asymptomatic family members is not likely to improve outcomes. It is unlikely that family members who do not exhibit developmental delay or other signs/symptoms of RTT will have a pathogenic mutation. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for genetic testing of individuals who have a child with RTT to determine carrier status in the preconception or prenatal period includes case series. Relevant outcomes are test accuracy and validity, other test performance measures, and changes in reproductive decision making. Carrier testing (preconception or prenatal) in a couple who have had a child with RTT or intellectual disability due to a MECP2 mutation is not likely to improve outcomes. The risk of a family having a second child with the disorder is less than 1%, except in the rare situation where the mother carries the mutation, and the impact on decision making is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added</td>
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<tr>
<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References