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

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.

Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

This is not a covered service.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)
MECP2 Genetic Testing Coding and Billing Guidelines (M00066, V5)
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.

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.

### Outpatient

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>No</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</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>
</tr>
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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>
</tr>
<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 among the most common genetic causes of intellectual disability in girls. RTT is characterized by apparent normal development for the first 6 to 18 months of life, followed by regression of intellectual functioning, acquired fine and gross motor skills, and social skills. Purposeful use of the hands is replaced by repetitive stereotyped hand movements, such as hand-wringing. Other clinical manifestations include seizures, disturbed breathing patterns with hyperventilation and periodic apnea, scoliosis, growth retardation, and gait apraxia.
There is wide variability in the rate of progression and severity of the disease. In addition to the classic form of RTT, there are 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. Diagnostic criteria for typical (or classic) RTT and atypical (or variant) RTT have been established.\textsuperscript{1-3} For typical RTT, a period of regression followed by recovery or stabilization and fulfillment of all the main criteria are required to meet the diagnostic criteria for classic RTT. For atypical RTT, a period of regression followed by recovery or stabilization, at least 2 of the 4 main criteria, plus 5 of 11 supportive are required to meet the diagnostic criteria of variant RTT.

**Treatment**

Currently, there are no specific treatments that halt or reverse disease progression, 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.\textsuperscript{1} A multidisciplinary approach is usually applied, with specialist input from dietitians, physical therapists, occupational therapists, speech therapists, and music therapists. Regular monitoring for scoliosis (seen in \approx 87\% of patients by age 25 years) and possible heart abnormalities, particularly cardiac conduction 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 to control 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 the MECP2 gene has demonstrated reversibility of the genetic defect.\textsuperscript{4,5}

**Genetics**

RTT is an X-linked dominant genetic disorder. Pathogenic variants 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 classic RTT have pathogenic variants in the MECP2 gene. More than 200 pathogenic variants in MECP2 have been associated with RTT.\textsuperscript{6} However, 8 of the most commonly occurring missense and nonsense variants account for almost 70\% of all cases; small C-terminal deletions account for approximately 10\%; and large deletions, 8\% to 10\%.\textsuperscript{7} MECP2 variant type is associated with disease severity.\textsuperscript{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.\textsuperscript{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 variant, 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 variant 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 variant in MECP2 does not necessarily equate to a diagnosis of RTT. Rare cases of MECP2 variants 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.\textsuperscript{1,6,11} Recent studies have revealed that different classes of genetic variants in MECP2 result in variable clinical phenotypes and overlap with other neurodevelopmental disorders.\textsuperscript{12-14}

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

**Summary**

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 (eg, MECP2, FOXG1, or CDKL5) in a patient with clinical features of RTT or in a patient’s family member.

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 versus 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 disease. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic sisters of an individual with RTT who receive targeted genetic testing for a known familial RTT-associated variant, the evidence 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 sisters of reproductive age, determination of carrier status can eliminate or necessitate prenatal testing and inform reproductive decision making. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are females with a child with RTT who are considering future childbearing who receive targeted genetic testing for a known familial RTT-associated variant, the evidence 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 that the technology results in a meaningful improvement in the net health outcome.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>12/2016</td>
<td>Non-coverage for Medicare Advantage clarified based on</td>
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</tbody>
</table>
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