MEDICAL POLICY – 12.04.81
Genetic Testing for Rett Syndrome

BCBSA Ref. Policy: 2.04.81
Effective Date: Aug. 1, 2018
Last Revised: July 25, 2018
Replaces: 2.04.81

RELATED MEDICAL POLICIES:
12.04.514 Genetic Testing for Epilepsy

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Rett syndrome is a rare disorder of the nervous system that affects mostly girls. This disorder influences how the brain develops. A girl with Rett syndrome grows normally for about the first six to eighteen months. Then, noticeable changes develop. The child’s loses the muscle ability she had already developed, so activities like crawling, walking, or using the hands begin to diminish. (Some boys also develop Rett syndrome but because of their chromosomal makeup they die before birth or as early in infancy.) A genetic change (mutation) is responsible for Rett syndrome. But this genetic change usually isn’t inherited from a parent. It most often occurs by chance. Rett syndrome can’t be cured. However, treatments can be used to help manage symptoms and provide support. Such care is usually needed throughout life. A genetic test is available to see if a person has Rett syndrome. This policy describes when the genetic test may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
### Service | Medical Necessity
--- | ---
**Genetic testing for Rett syndrome** | Genetic testing for Rett syndrome – associated genes (eg, MECP2, FOXG1, or CDKL5) may be considered medically necessary when the following criteria are met:
- 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** | Testing for that variant is medically necessary to determine carrier status of a mother or a sister of an individual with Rett syndrome.

### Service | Investigational
--- | ---
**All other indications for genetic testing for Rett syndrome – associated genes** | All other indications for genetic testing for Rett syndrome – associated genes (eg, MECP2, FOXG1, or CDKL5) are considered investigational including:
- Routine carrier testing (preconception or prenatal) in persons with negative family history of Rett syndrome
  **AND**
- Testing of asymptomatic family members to determine future risk of the disease

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>81302</td>
<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis</td>
</tr>
<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>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<td>81404</td>
<td>Molecular pathology procedure, Level 5 (e.g., 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 (e.g., 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>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
</tbody>
</table>

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**Related Information**

**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 1). 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 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

**Table 1. Nomenclature to Report on Variants Found in DNA**

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

**Table 2. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

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 the understanding of 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.

**Evidence Review**

**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 (eg, MECP2, FOXG1, or CDLK5) in a patient with clinical features of RTT or a patient’s family member.

Background

**Rett Syndrome**

Rett syndrome (RTT) is a severe neurodevelopmental disorder primarily affecting girls, with an incidence of 1 in 10,000 female births, making it among the most common genetic causes of intellectual disability in girls.¹ In its typical form, RTT is characterized by apparently 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 stereotypical hand movements, such as hand-wringing.³ 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 typical (or classic) form of RTT, there are recognized atypical variants. Three distinct atypical variants have been described: preserved speech, early seizure, and congenital variants. RTT occurring in males is also considered a variant type and is associated with somatic mosaicism or Klinefelter (XXY) syndrome. A small number of RTT cases in males arising from the MECP2 exon 1 variant have been reported. Diagnostic criteria for typical (or classic) RTT and atypical (or variant) RTT have been established.¹³ 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.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 ≈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, and 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.4,5

**Genetics**

RTT is an X-linked dominant genetic disorder. Pathogenic variants in the MECP2 gene, 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.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%, while large deletions are responsible for 8% to 10%.7 MECP2 variant 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 variant, which arises 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 a 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 having 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 have also 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 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 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, 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 and 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 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.

**Ongoing and Unpublished Clinical Trials**

Some trials that might influence this policy are listed in Table 3.

**Table 3. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
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<tr>
<td>NCT02061137</td>
<td>A Phase 1 Clinical Study to Assess Safety and Efficacy of Oral Fingolimod (FTY720) in Children With Rett Syndrome.</td>
<td>6</td>
<td>Jul 2018</td>
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<tr>
<td>NCT02171104</td>
<td>MT2013-31: Allogeneic Hematopoietic Cell Transplantation for Inherited Metabolic Disorders and Severe Osteopetrosis Following Conditioning With Busulfan (Therapeutic Drug Monitoring), Fludarabine +/- ATG</td>
<td>100</td>
<td>Sep 2019</td>
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<tr>
<td><strong>Unpublished</strong></td>
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<tr>
<td>NCT02023424</td>
<td>An Open Label, Exploratory Study to Investigate the Treatment Effect of Glatiramer Acetate (Copaxone ®) on Girls With Rett Syndrome</td>
<td>10</td>
<td>Feb 2015 (unknown)</td>
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<tr>
<td>NCT02153723</td>
<td>Pharmacological Treatment of Rett Syndrome With Glatiramer Acetate (Copaxone)</td>
<td>20</td>
<td>Jun 2015 (unknown)</td>
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<tr>
<td>NCT01777542</td>
<td>Pharmacological Treatment of Rett Syndrome by Stimulation of Synaptic Maturation With Recombinant Human IGF-1(Mecasermin [rDNA] Injection)</td>
<td>30</td>
<td>Nov 2016 (completed)</td>
</tr>
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</table>
**Clinical Input Received from Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input on the use of variant testing for Rett syndrome (RTT) was received from 2 specialty medical societies (3 reviewers) and 3 academic medical centers, for a total of 6 reviewers, while this policy was under review in 2012. There was consensus or near consensus supporting the use of variant testing for the diagnosis of RTT in a girl in whom the clinical differential diagnosis includes RTT, especially when clinical diagnosis is uncertain. Support for testing sisters of individuals with RTT and for prenatal screening was mixed.

**Practice Guidelines and Position Statements**

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


**American Academy of Pediatrics**

A 2007 policy statement27 from the American Academy of Pediatrics, reaffirmed in 201428, recommended *MECP2* testing to confirm a diagnosis of suspected Rett syndrome (RTT), especially when the diagnosis was unclear from symptoms alone.
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. ²⁹ 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 autistic spectrum disorders was not recommended.

**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.

**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 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.
References


## History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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</thead>
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<tr>
<td>09/11/12</td>
<td>New policy. Policy statements state that 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, but when there is uncertainty in the clinical diagnosis. All other indications for mutation testing for Rett syndrome, including prenatal screening and testing of family members, are considered investigational.</td>
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<td>01/14/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
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<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
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<tr>
<td>12/04/13</td>
<td>Replace Policy. Policy updated with a literature search through July 2013; references 3-6, 10 and 11 added. Policy statements unchanged. CPT codes 81404 and 81406 added as new codes specific to this policy.</td>
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<tr>
<td>01/03/14</td>
<td>Update Related Policies; add 12.04.109, effective 12/9/13.</td>
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<td>Comments</td>
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<tr>
<td>11/20/14</td>
<td>Annual Review. Policy updated with literature review through August 18, 2014; references 6, 8-11, 17, 19-22 added; reference 12 updated; others renumbered/removed. Policy statements unchanged.</td>
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<tr>
<td>06/16/15</td>
<td>Update Related Policies. 12.04.109 renumbered to 12.04.514.</td>
</tr>
<tr>
<td>12/08/15</td>
<td>Annual Review. Policy updated with literature review through October 31, 2015; no references added. Policy statement edited for clarity, no change to intent of policy statement.</td>
</tr>
<tr>
<td>12/01/16</td>
<td>Annual review, approved November 8, 2016. Review. Policy updated with literature review through September 2016; references added. Policy statement unchanged, format revisions only.</td>
</tr>
<tr>
<td>08/01/17</td>
<td>Annual review, approved July 18, 2017. Policy moved into new format. 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 limit populations to sisters of child with Rett syndrome (indication 2) or females with a child with Rett syndrome (indication 3) and revised to “targeted genetic testing for a known familial variant.” Policy statements updated to define &quot;genetic testing for Rett syndrome-- associated genes (eg, MECP2, FOXG1, or CDKL5)”; Removed “female” requirement of child for testing; Added 2 new medical necessity statements for &quot;targeted genetic testing for a known familial variant&quot; in a sister or mother of a child with Rett syndrome.</td>
</tr>
<tr>
<td>08/01/18</td>
<td>Annual Review, approved July 25, 2018. Policy updated with literature review through April 2018; references 23-24 added. Edits made to the investigational policy statement; statements otherwise unchanged.</td>
</tr>
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</table>

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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