## Genetic Testing for Rett Syndrome

Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

### Description

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.

### Summary of Evidence

MECP2 mutations are found in most patients with Rett syndrome (RTT), particularly those who present with classical clinical features of RTT. 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.

Testing for MECP2 mutations has clinical utility in certain clinical scenarios. The diagnosis of RTT is considered to be a clinical one, characterized by a specific developmental profile that should meet certain clinical diagnostic criteria. Certain atypical variants of RTT may be more difficult to diagnose clinically, and MECP2 mutation testing may be useful in confirming or excluding the diagnosis of RTT. Although there is no effective treatment for RTT, and management is mainly supportive, a definitive diagnosis can end a diagnostic workup for other possible diagnoses and may alter some aspects of management (e.g., determining whether or not to advise avoidance of medications that can prolong QT interval).

Testing of family members and prenatal testing 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 on health outcomes is uncertain.

Therefore, mutation testing for RTT may be considered medically necessary to confirm a diagnosis of RTT in a female child with developmental delay and signs/symptoms of RTT when there is uncertainty in the clinical diagnosis. All other indications for mutation testing for RTT, including prenatal screening and testing of family members, are considered investigational.

### Policy

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**Background**

**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. RTT is characterized by apparent normal development for the first six 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.

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.

**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. 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 (e.g., 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.

**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. However, eight 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%. MECP2 mutation type is associated with disease severity.
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.2, 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 FOXP1, have been shown to be associated with atypical variants.

Regulatory Status

No U.S. Food and Drug Administration-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.
