Rett syndrome (RTT), a neurodevelopmental disorder affecting almost exclusively females, is usually caused by variants in the \( MECP2 \) gene. Genetic testing is available to determine whether a pathogenic variant exists in a patient with clinical features of Rett syndrome, or in a patient's family member.

<table>
<thead>
<tr>
<th>MEDICAL POLICY CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Genetic testing for one or any combination of the following: ( MECP2 ), ( FOXG1 ), and ( CDKL5 ), for Rett syndrome may be considered <strong>medically necessary</strong> when all of the following criteria are met:</td>
</tr>
<tr>
<td>A. To confirm a diagnosis of Rett syndrome in a child with developmental delay and signs/symptoms of Rett syndrome; AND</td>
</tr>
<tr>
<td>B. When a definitive diagnosis cannot be made without genetic testing.</td>
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<tr>
<td>II. Targeted genetic testing for a known familial Rett-syndrome associated variant may be considered <strong>medically necessary</strong> to determine carrier status for an at-risk relative of an individual with Rett syndrome (see Policy Guidelines).</td>
</tr>
<tr>
<td>III. All other indications for genetic testing for Rett syndrome, including but not limited to prenatal screening, testing of other family members, and panel testing including genes</td>
</tr>
</tbody>
</table>
other than MECP2, FOXG1 and/or CDKL5 are considered investigational.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Relatives at risk for being asymptomatic carriers of Rett syndrome include first-degree relatives with two X-chromosomes (e.g., mothers and sisters of affected individuals).

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES
1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

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 Rett syndrome.[1-3]

**TREATMENT OF RETT SYNDROME**

There are currently 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 generally used, with specialist input from dietitians, physiotherapists, occupational therapists, speech therapists, and music therapists. Regular monitoring for scoliosis and possible heart abnormalities may be recommended. The development of scoliosis (seen in about 87% of patients by age 25 years) and the development of spasticity can have a major impact on mobility, and the development of effective communication strategies. Occupational therapy can help children develop skills needed for performing self-directed activities (such as dressing, feeding, and practicing arts and crafts), while physical therapy and hydrotherapy may prolong mobility.

Pharmacological 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.[4,5]

**GENETICS OF RETT SYNDROME**

Classic RTT results from an X-linked dominant condition. Variants in MECP2 (methyl-CpG-binding protein 2), which is thought to control expression of several genes including some involved in brain development, were first reported in 1999. Subsequent screening of RTT patients has shown that over 80% of classical RTT have pathogenic variants in the MECP2 gene. More than 200 variants in MECP2 have been described. However, eight 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%. [6] MECP2 variant type is associated with disease severity.[7] 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. In addition, the pattern of X-chromosome inactivation influences the severity of the clinical disease in females.

As 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).[8]

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% (since germline mosaicism in either parent cannot be excluded).

The 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.[1]

A proportion of patients with a clinical diagnosis of RTT do not appear to have variants in the MECP2 gene. Two other genes, CDKL5 and FOXG1, have been shown to be associated with atypical variants of RTT. Variants in CDKL5 are associated with a variant of RTT observed in females with apparently classic Rett syndrome in whom the presentation is dominated by seizures and onset is before age six months.[9] Variants in FOXG1 are associated with a type of RTT referred to as congenital or precocious RTT, in which regression is never clearly identified but the clinical picture is otherwise classic.[10]

REGULATORY STATUS

No U.S. Food and Drug Administration (FDA)-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.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[11] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

ANALYTIC VALIDITY

In 2015, the Agency for Healthcare Research and Quality (AHRQ) published results a
Technical Brief that addressed Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder.[12] The report summarizes information on genetic tests clinically available in the U.S. to detect genetic markers that predispose patients to developmental disabilities (DD). Input was sought from nine Key Informants to identify important clinical, technology, and policy issues from different perspectives. The National Center for Biotechnology Information's Genetic Testing Registry (GTR) was searched to identify genetic tests. The authors' search of the GTR database identified 672 laboratory-developed tests offered by 63 providers in 29 States. The authors found a limited number of studies reporting on the analytic validity of the DD genetic testing, but did identify one study citing analytic validity for RTT.[13]

In 2014, Kalman et al published results from a study that was conducted by the Centers for Disease Control and Prevention's Genetic Testing Reference Material Coordination Program, in collaboration with the genetic testing community and the Coriell Cell Repositories.[13] In this study the authors' established 27 new cell lines and characterized the MECP2 variants in these and in eight previously available cell lines. DNA samples from the 35 cell lines were tested by eight clinical genetic testing laboratories using DNA sequence analysis and methods to assess copy number (multiplex ligation-dependent probe amplification, semiquantitative PCR, or array-based comparative genomic hybridization). The eight common point variants known to cause approximately 60% of Rett syndrome cases were identified, as were other MECP2 variants, including deletions, duplications, and frame shift and splice-site variants.

In addition to the study by Kalman et al. discussed in the above AHRQ review, a large reference laboratory reports MECP2 testing for RTT has an analytical sensitivity for sequencing of 99% and for MLPA, 90%; analytic specificity is 99% for sequencing and for MLPA, 98%.[14]

CLINICAL VALIDITY

The AHRQ report, discussed above, reported that just one study was identified that addressed clinical validity, and it was not specific to RTT; however, there have been several small studies that were not included in the AHRQ report that discussed the clinical validity of genetic testing for RTT.[12]

Zhang (2018) investigated familial cases with RTT or X-linked mental retardation (XLMR).[15] For this study, 429 children were recruited from 427 Chinese families. Each child either had RTT or XLMR. All patients provided genomic DNA samples. Of the 427 families, three girls and five boys (from six families) were identified as having the MECP2 variant. The three girls met the diagnostic criteria for RTT; the five boys had XLMR. The MECP2 gene was sequenced and reviewers observed a random X-chromosome inactivation (XCI) pattern in all the girls and two of the mothers. A skewed XCI was seen in the other four mothers. In all MECP2 variant cases, the variant was confirmed to be an identical variant inherited from the mother. No variants were inherited from the father. This study adds to the relatively sparse literature on familial cases with MECP2 variants; with evidence for maternal inheritance of MECP2 variants.

Vidal (2017) investigated the utility of next-generation sequencing (NGS) and its ability to genetically identify an affected person.[16] To achieve the effect of NGS, several different techniques were employed, such as Sanger sequencing and whole-exome sequencing. This study included 1,577 patients who exhibited signs of having RTT but had not yet been formally diagnosed. Using Sanger sequencing, 1,341 patients were evaluated, and 26% had genes variants identified (RTT). Two hundred forty-two patients were assessed using the Haloplex
Custom Panel, and 22% were diagnosed genetically. Fifty-one patients were evaluated using the TruSight One panel, and 15 (29%) patients were diagnosed genetically; 25 patients were studied by whole-exome sequencing, and it was discovered that five variants occurred in genes previously associated with neurodevelopmental disorders with features similar to those of RTT syndrome. Reviewers conclude that NGS allows for more genes associated with RTT-like symptoms to be studied and therefore allows for a wider pool of patients to be studied, thus reducing cost and improving efficiency.

Halbach (2016) analyzed a cohort of a group of 132 well-defined RTT females aged between 2 and 43 years with extended clinical, molecular, and neurophysiological assessment.[17] Genotype-phenotype analyses of clinical features and cardiorespiratory data were performed after grouping variants by the same type and localization or having the same putative biological effect on the MeCP2 protein, and subsequently on eight single recurrent pathogenic variants. A less severe phenotype was seen in females with CTS, p.R133C, and p.R294X variants. Autonomic disturbances were present in all females, and not restricted to nor influenced by one specific group or any single recurrent variant. The objective information from non-invasive neurophysiological evaluation of the disturbed central autonomic control is of great importance in helping to organize the lifelong care for females with RTT. The study concluded that further research is needed to provide insights into the pathogenesis of autonomic dysfunction, and to develop evidence-based management in RTT.

Pidcock (2016) identified 96 RTT patients with pathogenic variants in the MECP2 gene.[18] Among 11 pathogenic variant groups, a statistically significant group effect of variant type was observed for self-care, upper extremity function, and mobility, on standardized measures administered by occupational and physical therapists. Patients with R133C and uncommon variants tended to perform best on upper extremity and self-care items, whereas patients with R133C, R306C and R294X had the highest scores on the mobility items. The worst performers on upper extremity and selfcare items were patients with large deletions, R255X, R168X, and T158M variants. The lowest scores for mobility were found in patients with T158M, R255X, R168X, and R270X variants. On categorical variables as reported by parents at the time of initial evaluation, patients with R133C and R294X were most likely to have hand use, those with R133C, R294X, R306C and small deletions were most likely to be ambulatory, and those with R133C were most likely to be verbal.

Sajan (2017) analyzed 22 RTT patients without apparent MECP2, CDKL5, and FOXG1 pathogenic variants were subjected to both whole-exome sequencing and single-nucleotide polymorphism array-based copy-number variant (CNV) analyses.[19] Three patients had MECP2 variants initially missed by clinical testing. Of the remaining 19, 17 (89.5%) had 29 other likely pathogenic intragenic variants and/or CNVs (10 patients had two or more). Interestingly, 13 patients had variants in a gene/region previously reported in other neurodevelopmental disorders (NDDs), thereby providing a potential diagnostic yield of 68.4%. The genetic etiology of RTT without MECP2, CDKL5, and FOXG1 variants is heterogeneous, overlaps with other NDDs, and complicated by a high variant burden. Dysregulation of chromatin structure and abnormal excitatory synaptic signaling may form two common pathological bases of RTT.

Maortua (2013) evaluated the presence of MECP2 variants (sequencing of four exons and rearrangements) in 120 female patients with suspected Rett syndrome, 120 female patients with intellectual disability of unknown origin and 861 (519 females and 342 males) controls.[20] Eighteen different pathological variants were identified in both patients suspected of Rett
syndrome and in those without a specific diagnosis. Authors concluded, “MECP2 must be studied not only in patients with classical/atypical Rett syndrome but also in patients with other phenotypes related to Rett syndrome.”

Two studies published in 2013 and 2012 respectively[21,22] used the InterRett database to examine genotype and RTT severity. Of 357 girls with epilepsy who had MECP2 genotype recorded, those with large deletions were more likely than those with 10 other common variants to have active epilepsy (odds ratio [OR]: 3.71 (95% confidence interval [CI]: 1.13, 12.17); p=0.03) and had the earliest median age at epilepsy onset (3 years 5 months). Among all girls in the database, those with large deletions were more likely to have never walked (OR: 0.42 (95% CI: 0.22, 0.79), p=0.007). Among 260 girls with classic RTT enrolled in the multicenter RTT Natural History study, those with the R133C substitution variant had clinically less severe disease, assessed by the Clinical Severity, Motor Behavior Analysis, and Physician Summary scales.[6] Fabio et al reported similar genotype-phenotype correlations among 144 patients with RTT in Italy.[23]

Huppke (2009) analyzed the MECP2 gene in 31 female patients diagnosed clinically with RTT.[24] Sequencing revealed variants in 24 of the 31 patients (77%). Of the seven patients in whom no variants were found, five fulfilled the criteria for classical RTT. In this study, 17 different variants were detected, 11 of which had not been previously described. Several females carrying the same variant displayed different phenotypes, suggesting that factors other than the type or position of variants influence the severity of RTT.

Lotan (2006) reviewed and summarized six articles that attempted to disclose a genotype-phenotype correlation, which included the two studies outlined above.[2] The authors found that these studies have yielded inconsistent results and that further controlled studies are needed before valid conclusions can be drawn about the effect of variant type on phenotypic expression.

A study by Cheadle (2000) analyzed variants in 48 females with classical sporadic RTT, seven families with possible familial RTT, and five sporadic females with features suggestive, but not diagnostic, of RTT.[25] The entire MECP2 gene was sequenced in all cases. Variants were identified in 44/55 (80%) of unrelated classical sporadic and familial RTT patients. Only one out of five (20%) sporadic cases with suggestive but non-diagnostic features of RTT had variants identified. Twenty-one different variants were identified (12 missense, four nonsense, and five frame-shift variants); 14 of the variants identified were novel. Significantly milder disease was noted in patients carrying missense variants as compared to those with truncating variants.

Section Summary

Although the AHRQ report reported finding no studies on clinical validity for RTT, there is evidence from several small studies indicates that the clinical sensitivity of genetic testing for classical RTT is reasonably high, in the range of 75 to 80%. However, the sensitivity may be lower when classic features of RTT are not present. The clinical specificity is unknown but is also likely to be high, as only rare cases of MECP2 variants have been reported in other clinical phenotypes, including individuals with an Angelman-like picture, nonsyndromic X-linked intellectual disability, PPM-X syndrome, autism and neonatal encephalopathy.

CLINICAL UTILITY
The AHRQ report found that the majority of the clinical studies identified for RTT were for indirect assessment of clinical utility as “most of the genetic tests relevant to this report are intended to establish an etiologic diagnosis and rarely used in isolation to confirm a clinical diagnosis”. Finally, no studies were identified that directly assessed the impact of genetic testing on health outcomes.

However, the clinical utility of genetic testing can be considered in the following clinical situations: 1) individuals with suspected RTT, 2) family members of individuals with RTT, and 3) prenatal testing for mothers with a previous RTT child. These situations are discussed separately below.

**Individuals with Suspected RTT**

The clinical utility for these patients depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes. No studies were identified that described how a molecular diagnosis of RTT changed patient management. Therefore, there is no direct evidence for the clinical utility of genetic testing in these patients.

Given that there is no specific treatment for RTT, making a definitive diagnosis will not lead to treatment that alters the natural history of the disorder. However, there are several potential ways in which adjunctive management might be changed following genetic testing after confirmation of the diagnosis:

- Further diagnostic testing may be avoided
- Referral to a specialist(s) may be made
- Heightened surveillance for Rett-associated clinical manifestations, such as scoliosis or cardiac arrhythmias may be performed
- More appropriate tailoring of ancillary treatments such as occupational therapy may be possible

Therefore, genetic testing for RTT syndrome in developmentally delayed female children, without a clear diagnosis, may offer some surveillance benefits as well as help to avoid unnecessary additional diagnostic testing.

**Family Member and Prenatal RTT Testing**

Genetic testing can be done in sisters of girls with RTT who have an identified MECP2 pathogenic variant to determine if they are asymptomatic carriers of the disorder. However, this is an extremely rare possibility, since the disorder is nearly always sporadic. Testing of family members of individuals with RTT will therefore result in an extremely low yield. However, testing for a known familial Rett-syndrome-associated variant may aid mothers and sisters of affected individuals in reproductive decision-making.

Similarly, in cases of prenatal testing 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 variant. Therefore, for mothers without the Rett phenotype, it is extremely unlikely that prenatal testing will identify cases of RTT.

**Section Summary**

The clinical utility of genetic testing for RTT has not been established in the literature; however,
genetic testing can confirm a diagnosis in patients with clinical signs and symptoms of Rett syndrome. A definitive diagnosis may help avoid further testing for other possible syndromes as well as alter surveillance and management of Rett associated conditions. While direct evidence of clinical utility for family member and prenatal testing is lacking, there may be some benefit in terms of reproductive decision making.

**PRACTICE GUIDELINE SUMMARY**

No evidence-based clinical practice guidelines were identified which gave recommendations on when to perform CDKL5 or FOXG1 testing. However, studies have suggested that patients who are negative for MECP2 variants and who have a strong clinical diagnosis of RTT should be considered for further screening of the CDKL5 gene if there are early-onset seizures, or the FOXG1 gene if there are congenital features (e.g., severe postnatal microcephaly).[1-3]

**AMERICAN ACADEMY OF NEUROLOGY AND THE PRACTICE COMMITTEE OF THE CHILD NEUROLOGY SOCIETY**[27]

In 2011, a quality standards subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society issued an evidence report on the genetic and metabolic testing of children with global developmental delay. The report concluded, “Girls with severe impairment may be appropriate for testing for MECP2 mutations, regardless of whether the specific clinical features of Rett syndrome are present.”

**AMERICAN ACADEMY OF PEDIATRICS**[28,29]

In 2014 the American Academy of Pediatrics (AAP) reaffirmed earlier their recommendation for MECP2 testing to confirm a diagnosis of suspected Rett syndrome in females, especially when the diagnosis is unclear from symptoms alone.

**AMERICAN COLLEGE OF MEDICAL GENETICS**

In 2013, ACMG updated their guideline for the genetic evaluation of autism spectrum disorders. Testing for MECP2 variants is recommended as part of the diagnostic workup of females who present with an autistic phenotype.[30] Routine MECP2 testing in males with autistic spectrum disorders is not recommended.

**SUMMARY**

There is enough research to show that genetic testing for variants in MECP2, FOXG1 and/or CDKL5 may be useful in confirming or excluding the diagnosis of Rett syndrome (RTT). Although there is no effective treatment for RTT, a definitive diagnosis can end a diagnostic workup for other possible diagnoses and may alter some aspects of management. Therefore, genetic testing of the MECP2, FOXG1 and/or CDKL5 genes for RTT may be considered medically necessary in select patients who meet the policy criteria.

There is enough research to show that genetic testing for Rett syndrome (RTT) variants in at-risk relatives of patients with RTT may help with reproductive decision-making. Therefore, targeted genetic testing of known familial RTT variants may be considered medically necessary for these individuals.
There is not enough research to show that genetic testing for Rett syndrome (RTT) can improve health outcomes or reproductive decision-making in situations that do not meet the policy criteria. Also, *MECP2*, *FOXL1* and *CDKL5* are the only genes that have been shown to cause RTT. Therefore, genetic testing for Rett syndrome is considered investigational for all other indications, including but not limited to prenatal screening and panel testing that includes genes other than *MECP2*, *FOXL1* and/or *CDKL5*.

**REFERENCES**


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<tr>
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<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis</td>
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| HCPCS | None |

*Date of Origin: May 2010*