Genetic Testing for Rett Syndrome

Policy # 00369
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider mutation testing for Rett syndrome (RTT) to confirm a diagnosis of Rett syndrome (RTT) in a female child with developmental delay and signs/symptoms of Rett syndrome (RTT), but when there is uncertainty in the clinical diagnosis, to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers all other indications for mutation testing for Rett syndrome (RTT), including prenatal screening and testing of family members, to be investigational.*

Background/Overview
Rett syndrome, a neurodevelopmental disorder, is usually caused by mutations in the methyl-CpG-binding protein 2 (MECP2) 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.

Rett Syndrome
Rett syndrome 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. Rett syndrome is characterized by apparent normal development for the first 6-18 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 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. A multidisciplinary approach is usually 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. Rett syndrome 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.

**Genetics of Rett Syndrome**

Rett syndrome results from an X-linked dominant condition. 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 of RTT patients has shown that over 80% of classical RTT have pathogenic mutations in the MECP2 gene. More than 200 mutations in MECP2 have been described. 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, 8–10%. Whole duplications of the MECP2 gene have been associated with severe X-linked mental retardation 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).

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 mental retardation). 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% (since germline mosaicism in either parent cannot be excluded).
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The identification of a mutation in MECP2 does not necessarily equate to a diagnosis of RTT. Rare cases of MECP2 mutations have also been reported in other clinical phenotypes, including individuals with an Angelman-like picture, nonsyndromic X-linked mental retardation, PPM-X syndrome (an X-linked genetic disorder characterized by psychotic disorders [most commonly bipolar disorder], parkinsonism, and mental retardation), autism and neonatal encephalopathy.

A proportion of patients with a clinical diagnosis of RTT do not appear to have mutations in the MECP2 gene. Two other genes, cyclin-dependent kinase-like 5 (CDKL5) and forkhead box protein G1 (FOXG1), have been shown to be associated with atypical variants.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
No U.S. 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.

Rationale/Source
Literature that describes the analytic validity, clinical validity, and clinical utility of genetic testing for RTT was sought.

Analytic Validity (the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent)

The test is generally done as full gene sequencing of the MECP2 gene to diagnose atypical or classic RTT and as multiplex ligation probe amplification (MLPA) for duplication/deletion analysis. Familial mutation testing may be done with targeted sequencing. CDKL5 sequencing may be done for atypical RTT.

According to a large reference laboratory, 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%.

Clinical Validity (the diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease)

Huppke and colleagues analyzed the MECP2 gene in 31 female patients diagnosed clinically with RTT. Sequencing revealed mutations in 24 of the 31 patients (77%). Of the 7 patients in whom no mutations were found, 5 fulfilled the criteria for classical RTT. In this study, 17 different mutations were detected, 11 of which had not been previously described. Several females carrying the same mutation displayed different phenotypes, suggesting that factors other than the type or position of mutations influence the severity of RTT.
Cheadle and colleagues analyzed mutations in 48 females with classical sporadic RTT, 7 families with possible familial RTT, and 5 sporadic females with features suggestive, but not diagnostic, of RTT. The entire MECP2 gene was sequenced in all cases. Mutations were identified in 44/55 (80%) of unrelated classical sporadic and familial RTT patients. Only 1 out of 5 (20%) sporadic cases with suggestive but non-diagnostic features of RTT had mutations identified. Twenty-one different mutations were identified (12 missense, 4 nonsense, and 5 frame-shift mutations); 14 of the mutations identified were novel. Significantly milder disease was noted in patients carrying missense mutations as compared to those with truncating mutations.

Lotan and colleagues (2006) summarized 6 articles that attempted to disclose a genotype-phenotype correlation, which included the 2 studies outlined above. 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 mutation type on phenotypic expression. Two subsequent studies 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 mutations 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 (NCT00299312), those with the R133C substitution mutation had clinically less severe disease, assessed by the Clinical Severity, Motor Behavior Analysis, and Physician Summary scales.

Conclusions:
Evidence from several small studies indicates that the clinical sensitivity of genetic testing for classical RTT is reasonably high, in the range of 75-80%. 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 mutations have been reported in other clinical phenotypes, including individuals with an Angelman-like picture, nonsyndromic X-linked mental retardation, PPM-X syndrome, autism and neonatal encephalopathy.

Clinical Utility (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 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 will be discussed separately below.

Individuals with Suspected Rett Syndrome
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.
There is no specific treatment for RTT, so that making a definitive diagnosis will not lead to treatment that alters the natural history of the disorder. 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

Family Members
Genetic testing can be done in sisters of girls with RTT who have an identified MECP2 mutation 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.

Prenatal Screening.
It may be appropriate to offer prenatal diagnosis to a couple who have had a child with RTT or mental retardation due to a MECP2 mutation. Because the disorder occurs spontaneously in most affected individuals, however, 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. Therefore, for mothers without the Rett phenotype, it is extremely unlikely that prenatal testing will identify cases of RTT.

Conclusions
The clinical utility of genetic testing for RTT has not been established in the literature, however, genetic testing can confirm the diagnosis in patients with clinical signs and symptoms of RTT, and management changes may result. In addition, a definitive diagnosis can avoid further testing for other possible diagnoses. For testing family members and for prenatal testing, the clinical utility is lacking, since the yield of testing in those situations is extremely low.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received related to the use mutation testing for RTT in June 2012 from 3 academic medical centers and 2 specialty medical societies (3 reviewers), for a total of 6 reviewers. While the various physician specialty societies and academic medical centers may 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.

There was consensus/near total consensus supporting the use of mutation testing for the diagnosis of RTT in a girl in whom the clinical differential diagnosis includes RTT, especially when the clinical diagnosis is uncertain. Support for testing sisters of individuals with RT and for prenatal screening was mixed.
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Ongoing Clinical Trials
Online site, ClinicalTrials.gov, currently lists several active trials of treatments for RTT: EPI-743, an experimental antioxidant for treatment of mitochondrial disorders (NCT01822249); recombinant insulin-like growth factor-1 (NCT01253317, NCT01777542); and dextromethorphan (NCT01520363).

Summary
MECP2 mutations are found in the majority of 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 gold standard for the diagnosis of RTT, but 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 mental retardation 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.

References

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Next Scheduled Review Date: 11/2014

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
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B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
   A. in accordance with nationally accepted standards of medical practice;
   B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
   C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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