Genetic Testing for Rett Syndrome

**Description of Procedure or Service**

Rett syndrome, 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 Rett syndrome, or in a patient’s family member.

**Rett Syndrome**

Rett syndrome (RTT) is a severe neurodevelopmental disorder primarily affecting females with an incidence of 1:10,000 female births, making it one of the most common genetic causes of severe mental retardation in females. RTT 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. (1) 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 Rett syndrome.

**Treatment of Rett Syndrome**

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 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). Spasticity can have a major impact on mobility, physical therapy and hydrotherapy may prolong mobility.

Occupational therapy can help children develop skills needed for performing self-directed activities (such as dressing, feeding, and practicing arts and crafts). 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.
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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 Rett Syndrome

RTT results from an X-linked dominant genetic disorder. Mutations 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 mutations in the MECP2 gene. More than 200 mutations in MECP2 have been described, however, eight of the most commonly occurring missense and nonsense mutations account for almost 70% of all. Small C-terminal deletions account for 10% of cases and large deletions, 8%-10%. MECP2 mutation type is associated with disease severity. 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.

Because the spectrum of clinical phenotypes is broad, to facilitate genotype-phenotype correlation analyses, 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).

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, CDKL5 and FOXG1, have been shown to be associated with atypical variants.

Regulatory Status

No 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 highComplexity testing.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.
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Policy

BCBSNC will provide coverage for genetic testing for Rett syndrome when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Rett Syndrome is covered

Genetic 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, a definitive diagnosis cannot be made with genetic testing.

When Genetic Testing for Rett Syndrome is not covered

All other indications for mutation testing for Rett syndrome, including prenatal screening and testing of asymptomatic family members to determine future risk of disease, are considered investigational.

Policy Guidelines

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 percent, except in the rare situation where the mother carries the mutation, and the impact on decision making on health outcomes is uncertain.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81302, 81303, 81304
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BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Medical Director review 7/2012

Specialty Matched Consultant Advisory Panel review 1/2013


Specialty Matched Consultant Advisory Panel review 1/2014


Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Medical Director review 3/2016

Policy Implementation/Update Information

8/21/12 New policy developed. Genetic testing for Rett syndrome may be considered medically necessary to confirm a diagnosis of Rett syndrome in a female child with developmental
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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. Medical Director
(mco)

2/12/13 Specialty Matched Consultant Advisory Panel review 1/2013. Added related policy to Description
section. No changes to Policy Statements. (mco)

10/29/13 Description section updated. References updated. No changes to Policy Statements. (mco)

2/25/14 Specialty Matched Consultant Advisory Panel review 1/2014. No changes to Policy
Statements. (mco)

11/11/15 Description section updated. References updated. No change to Policy Statements. (td)

5/26/15 Specialty Matched Consultant Advisory Panel review 4/2015. Medical Director review
4/2015. No changes to Policy Statements. (td)

4/29/16 When Covered and When Not Covered sections revised for clarity, no change to intent of
review 3/2016. Medical Director review 3/2016. (td)

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