Genetic Testing for Rett Syndrome

Rett syndrome (RTT), a neurodevelopmental disorder, is usually caused by pathogenic variants in the MECP2 (methyl-CpG-binding protein 2) gene. Genetic testing is available to determine whether a pathogenic variant exists in RTT-associated genes, such as MECP2, FOXL1, or CDLK5, in a patient with clinical features of RTT, 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 intellectual disability 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. 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 classic 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. Diagnostic criteria for typical (or classic) RTT and atypical (or variant) RTT have been established. For typical RTT, a period of regression followed by recovery or stabilization and fulfillment of all 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 out of the 4 main criteria plus 5 out of 11 supportive are required to meet the diagnostic criteria of variant RTT.

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, physical therapists, occupational therapists, speech therapists and music therapists. Regular monitoring for scoliosis (seen in approximately 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; physical therapy and hydrotherapy may prolong mobility. Occupational therapy can help children develop communication strategies and skills needed for performing self-directed activities (such as dressing, feeding, and practicing arts and crafts).
Genetic Testing for Rett Syndrome

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 Rett Syndrome

RTT is an X-linked dominant genetic disorder. Pathogenic 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 classic RTT have pathogenic variants in the MECP2 gene. More than 200 pathogenic variants in MECP2 have been associated with RTT, 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% of cases and large deletions, 8%-10%. MECP2 variant 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. 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 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. Recent studies have revealed that different classes of genetic variants in MECP2 result in variable clinical phenotypes and overlap with other neurodevelopmental disorders.

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

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for Rett syndrome is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for
Genetic Testing for Rett Syndrome

high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

***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.

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-associated genes (eg. MECP2, FOXG1, or CDKL5) may be considered medically necessary 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 may be considered medically necessary to determine carrier status of a mother or a sister of an individual with Rett syndrome.

When Genetic Testing for Rett Syndrome is not covered

All other indications for genetic testing for Rett syndrome-associated genes (eg. MECP2, FOXG1, or CDKL5), including carrier testing (preconception or prenatal), and testing of asymptomatic family members to determine future risk of disease, are considered investigational.

Policy Guidelines

The evidence for genetic testing for RTT-associated genes in individuals who have signs and/or symptoms of Rett syndrome (RTT), 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 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 presentation of typical versus atypical RTT, but testing appears to have high sensitivity and specificity. Genetic testing has clinical utility when signs and symptoms of Rett syndrome 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.

The evidence for targeted genetic testing of asymptomatic sisters of an individual with RTT with a known familial RTT-associated variant, 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
Genetic Testing for Rett Syndrome

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.

The evidence for targeted genetic testing of a known familial Rett syndrome-associated variant for individuals who are females and have a child with RTT and are considering future childbearing, includes case 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 of 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% chance 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.

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, 81404, 81405, 81406

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


Genetic Testing for Rett Syndrome


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

Specialty Matched Consultant Advisory Panel review 3/2017
Medical Director review 3/2017


Medical Director review 5/2017
Specialty Matched Consultant Advisory Panel review 3/2018
Medical Director review 3/2018

**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 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 review 7/2012. Notification given August 21, 2012 for effective date of November 27, 2012. (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)
Genetic Testing for Rett Syndrome


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


4/28/17 When Covered section, removed the sentence “a definitive diagnosis cannot be made with genetic testing”. Minor updates to Description section; Regulatory status updated. Policy guidelines extensively updated. No change to policy intent. Specialty Matched Consultant Advisory Panel review 3/2017. Medical Director review 3/2017. (jd)

6/30/17 Policy updated with current genetic nomenclature, “mutations” changed to “variants”. Policy statement revised to include “genetic testing” for Rett-syndrome associated genes (MECP2, FOXL1 or CDKL5); removed “female” requirement for testing. Added new medical necessity statement for “targeted genetic testing for a known familial variant” in a mother or sister of an individual with Rett syndrome” to “When Covered” section. Revised “When Not Covered” section to include “Rett syndrome-associated genes”. Policy guidelines updated to support policy statements. References updated. Medical Director review 5/2017. (jd)

1/26/18 Added codes 81404, 81405, 81406 to code section. No change to policy intent.(jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.