Description of Procedure or Service

Rett syndrome (RTS) is a rare X-linked neurodevelopmental disorder usually caused by mutations in the Methyl CpG binding protein 2 (MECP2) gene (Amir et al., 1999). Affecting girls almost exclusively, it is characterized by normal early growth and development followed by regressions in development, walking, language, and purposeful use of the hands, along with slowed brain and head growth, distinctive hand movements, seizures, and intellectual disability (Colvin et al., 2004; Hagberg, Aicardi, Dias, & Ramos, 1983; Leonard, Cobb & Downs, 2017; Naidu, Murphy, Moser, & Rett, 1986; Neul et al., 2010; Rett, 1966).

***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 the medical criteria or reimbursement guidelines 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 MECP2, CDKL5 and/or FOXG1 mutation on the X chromosome of a child with developmental delay/intellectual disability and signs/symptoms of Rett syndrome is covered to confirm a diagnosis when there is uncertainty in the clinical diagnosis.

When Genetic Testing for Rett Syndrome is not covered

All other indications for mutations testing for Rett syndrome, including prenatal screening and testing of family members are not covered.

Policy Guidelines

Background

RTS is a severe neurodevelopmental disorder which affects approximately 1:10,000 live female births (Hagberg, 1985). It is a prominent cause of severe intellectual disability in women which accounts for up to 10% of cases with genetic origin (Armstrong, 1997). Originally thought to be
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lethal in males (Amir et al., 1999; Franco & Ballabio, 2006), it has been identified in up to 1.3% of male patients with mental retardation (Villard, 2007) and can be associated with a more severe phenotype (Q. Zhang et al., 2017).

RTS can be inherited as an X-linked dominant disorder, however more than 99% of cases result from a de novo pathogenic mutation in the MECP2 gene (Amir et al., 1999; Christodoulou & Ho, 1993), a transcriptional regulator located on the X chromosome. More than 200 mutations in MECP2 have been associated with RTS (Suter, Treadwell-Deering, Zoghbi, Glaze, & Neul, 2014). Analysis of parental origin of the mutated MECP2 gene in sporadic cases of RTS showed that 94.4% mutations were from paternal origin, 90.6% of which were point mutations, and 5.6% were from maternal origin (X. Zhang et al., 2012), which may explain the high occurrence of RTS in female gender. MeCP2 is a multifunctional protein which interprets DNA methylation and regulates chromatin architecture, gene transcription and RNA splicing (Sun et al., 2018). The complex upstream and downstream pathways of MECP2 involve microRNAs and neurotrophic factors such as GABA and BDNF (Kang, Kim, Johnston, & Kadam, 2014).

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MECP2 is critical for neuronal maturation (Fukuda, Itoh, Ichikawa, Washiyama, & Goto, 2005; Smrt et al., 2007) and its deficiency results in impaired dendritic morphogenesis and reduced dendritic spine numbers (Chapleau et al., 2009; Kishi & Macklis, 2010) resulting in dysfunctional synaptic transmission and neural network activity (Sun et al., 2018) affecting successive stages of brain development including prenatal neurogenesis, postnatal development of synaptic connections and function, experience-dependent synaptic plasticity, and maintenance of adult neural function including sensory integration (Feldman, Banerjee, & Sur, 2016). The clinical picture of RTS is characterized by a broad clinical spectrum of signs and symptoms and a distinctive course (Pini et al., 2016) of apparent normal development for the first 6 to 18 months of life, followed by characteristic developmental stagnation and loss of acquired skills including loss of intellectual functioning, loss of acquired fine and gross motor skills and communication (Colvin et al., 2004; Dolce, Ben-Zeev, Naidu, & Kossoff, 2013; Hagberg et al., 1983; Leonard et al., 2017; Naidu et al., 1986; Neul et al., 2010; Rett, 1966). Purposeful use of the hands is often replaced by repetitive stereotypical hand movements (Dy et al., 2017; Elian & de, 1996; Goldman & Temudo, 2012). Other clinical observations include deceleration of head growth, seizures, disturbed breathing patterns, scoliosis, growth retardation and gait apraxia (Cianfaglione et al., 2015).

Despite this period of apparently normal early development these profound neurological regressions have been found to result from MECP2 related defects in the establishment and refinement of early neural circuits and, later, cortical plasticity (Feldman et al., 2016) and subtle signs such as hypotonia, jerkiness in limb movement and limited social interaction can be present during early infancy (Ip, Mellios, & Sur, 2018).

The severity and rate of progression of this disease can vary greatly, and there are several recognized atypical variants. The milder forms (Zappella) present with less severe regression and milder expression of the clinical characteristics of RTS. In the most severe forms there is no normal development period (Neul et al., 2010). Both genetic and clinical variants of RTS are associated with distinct electrophysiological profiles reflecting how genetic dysregulation of synapse formation results in differences in neuronal network architecture (Sun et al., 2018) and produces the varying clinical phenotypes (Keogh et al., 2018). The pattern of X-chromosome inactivation can also influence the severity of the clinical disease (Archer et al., 2007; Weaving et al., 2003).

Mutations in the upstream cyclin-dependent kinase-like 5 (CDKL5) gene causes an early seizure (Hanefield) variant of the RTS phenotype(Bahi-Buisson et al., 2008), and mutations in the forkhead box G1 (FOXG1) gene have been found in the congenital variant (Rolando)(Ariani et
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al., 2008). Two cases of females with pathogenic de novo mutations in SCN1A, which usually leads to Dravet syndrome, but fulfill the diagnostic criteria for classic RTS have also been reported (Henriksen, Ravn, Paus, von Tetzchner, & Skjeldal, 2018). MECP2 duplication presents in males as phenotype consisting of infantile hypotonia, recurrent respiratory infections and severe mental retardation (Villard, 2007).

Applicable Federal Regulations

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found.

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories. LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements
American Academy of Neurology/Child Neurology Society

In 2011, a quality standards subcommittee of American Academy of Neurology (AAN) 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. AAN recommended considering MECP2 mutation testing for all girls with unexplained moderate to severe developmental delay. Males with a history strongly suggestive of X-linked inheritance may be considered for testing of one or more individual XLID genes or for screening of the entire X chromosome (Michaelson, 2011).

American Academy of Pediatrics

A 2014 policy statement from the American Academy of Pediatrics (AAP) recommends MECP2 mutation analysis for girls with microcephaly or deceleration of head growth and other features of Rett syndrome, or who present with stereotypical hand-wringing movements and developmental regression. MECP2 gene mutations are extremely rare in males but may be considered in boys who present with clinical features of Rett syndrome or severe developmental regression. (Moeschler, 2014)

Complete MECP2 deletion, duplication, and sequencing study is also recommended for females with intellectual disability or global developmental delay for whom the chromosomal microarray, specific metabolic testing, and fragile X genetic testing did not produce a diagnosis (Moeschler & Shevell, 2014).

RettSearch

Neither AAN nor AAP have provided recommendations on when to use CDKL5 or FOXG1 testing. RettSearch members, representing the majority of the international clinical RTS specialists, participated in an iterative process to come to a consensus on a revised and simplified clinical diagnostic criteria for RTS (Neul et al., 2010). This group provided clarifications for diagnosis of classic or typical RTS and atypical RTS and provided guidelines for molecular evaluation of specific variant forms of RTS. The authors define RTS as a clinical diagnosis based on distinct clinical criteria, independent of molecular findings. Presence of a MECP2 mutation is not sufficient for the diagnosis of RTS. Neul and colleagues did propose three distinct criteria for diagnosis of variant forms of RTS: preserved speech variant (Zapella variant), early seizure variant (Hanefeld variant) and congenital variant (Rolando variant) and recommended identifying molecular genetics of each variant. In the Zapella variant, the molecular analysis for MECP2 was
recommended. In Hanefeld and Rolando variants, analysis for mutations in CDKL5 for Hanefeld variant and in FOXG1 for Rolando variant were recommended. They also suggested that patients who are negative for MECP2 mutations and who have a strong clinical diagnosis of RTS should be considered for further screening for the CDKL5 gene if there are early onset seizures or for the FOXG1 gene if there are congenital features (e.g., severe postnatal microcephaly).

American College of Medical Genetics

In 2013, the American College of Medical Genetics revised its evidence-based guideline for clinical genetics evaluation of autism spectrum disorders. Testing for MECP2 mutations is recommended as part of the diagnostic workup of females who present with an autistic phenotype. Routine MECP2 testing in males with autistic spectrum disorders is not recommended. However, when features of MECP2 duplications (e.g., drooling, recurrent respiratory infections, hypotonic facies) are present consider MECP2 duplication testing in boys with autism and such features. (Schaefer & Mendelsohn, 2013)

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


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Policy Implementation/Update Information

1/1/2019 BCBSNC will provide coverage for genetic testing for Rett syndrome when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

4/1/2019 Description section, policy guidelines and references updated. Medical Director review 4/2019. (jd)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)
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2/11/20 Annual review by Avalon 4th Quarter 2019 CAB. No revisions and no change to policy intent. Medical Director review 12/2019. (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.