The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**Description**

Rett syndrome (RTT), a neurodevelopmental disorder, is usually caused by mutations in the MECP2 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.

**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 six 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, 2)

**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 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, 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.

**Genetics of Rett syndrome**

RTT results from an X-linked dominant condition. 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. 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, a locus-specific International Rett Syndrome Association MECP2 variation database has been established.

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 percent of total cases, 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, autism and neonatal encephalopathy. (1)

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 Netrin G, have been shown to be associated with a phenotype that strongly overlaps that seen in RTT.

**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 high-complexity testing.

**Corporate Medical Guideline**

Mutation 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.
Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.