BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.81 Genetic Testing for Rett Syndrome

Effective Policy Date: October 1, 2023

Original Policy Date: December 2012

Related Policies:

None

Genetic Testing for Rett Syndrome

Description

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Rett syndrome (RTT), a neurodevelopmental disorder, is usually caused by pathogenic variants in the methyl-CpG-binding protein 2 (MECP2) gene. Genetic testing is available to determine whether a pathogenic variant exists in RTT-associated genes (eg, MECP2, FOXG1, or CDLK5) in an individual with clinical features of RTT or an individual's family member.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for Rett (RTT)-associated genes improves the net health outcome in individuals with signs and/or symptoms of RTT, who are asymptomatic sisters of a child with RTT with a known pathogenic variant, or women with a child with RTT with a known pathogenic variant who are considering further childbearing.

POLICY STATEMENT

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.

POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for Rett syndrome is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have signs and/or symptoms of Rett syndrome (RTT) who receive genetic testing for RTT-associated genes, the evidence 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. Methyl-CpG-binding protein 2 (*MECP2*) variants are found in most patients with RTT, particularly in 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 presentations of typical versus atypical RTT, but testing appears to have high sensitivity and specificity. Genetic testing has clinical utility when signs and symptoms of RTT 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 the disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic sisters of an individual with RTT who receive targeted genetic testing for a known familial RTT-associated variant, the evidence includes case series and prospective cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, changes in reproductive decision making, symptoms, 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 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 an improvement in the net health outcome.

For individuals who are females with a child with RTT who are considering future childbearing who receive targeted genetic testing for a known familial RTT-associated variant, the evidence includes cases 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% of being affected, with males typically presenting with more severe disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology and Child Neurology Society

In 2011, the American Academy of Neurology and the Child Neurology Society issued an evidence report on genetic and metabolic testing of children with global developmental delay.[27,] The 2 societies recommended considering methyl-CpG-binding protein 2 (*MECP2*) genetic testing for all girls with unexplained moderate-to-severe developmental delay.

American Academy of Pediatrics

In 2007, the American Academy of Pediatrics (AAP) issued a policy statement (reaffirmed in 2014 and 2019)[28,29,] recommending *MECP2* testing to confirm a diagnosis of suspected Rett syndrome (RTT), especially when the diagnosis was unclear from symptoms alone.

In 2020, the AAP published Clinical Report Guidance on the identification, evaluation, and management of children with autism spectrum disorder which stated that "if patient is a girl, consider evaluation for Rett syndrome, MECP2 testing."[30,]

Neither the American Academy of Neurology nor the American Academy of Pediatrics has provided recommendations on when to use *CDKL5* or *FOXG1* testing.

American College of Medical Genetics and Genomics

In 2013, the American College of Medical Genetics and Genomics revised its evidence-based guidelines for clinical genetics evaluation of autism spectrum disorders.[31,] Testing for *MECP2* genetic variants was recommended as part of the diagnostic workup of females who present with an autistic phenotype. Routine *MECP2* testing in males with autism spectrum disorders was not recommended.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Williamson SL, Christodoulou J. Rett syndrome: new clinical and molecular insights. Eur J Hum Genet. Aug 2006; 14(8): 896-903. PMID 16865103
2. Petriti U, Dudman DC, Scosyrev E, et al. Global prevalence of Rett syndrome: systematic review and meta-analysis. Syst Rev. Jan 16 2023; 12(1): 5. PMID 36642718
3. Lotan M, Ben-Zeev B. Rett syndrome. A review with emphasis on clinical characteristics and intervention. ScientificWorldJournal. Dec 06 2006; 6: 1517-41. PMID 17160339
4. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. Dec 2010; 68(6): 944-50. PMID 21154482
5. Guy J, Gan J, Selfridge J, et al. Reversal of neurological defects in a mouse model of Rett syndrome. Science. Feb 23 2007; 315(5815): 1143-7. PMID 17289941
6. Robinson L, Guy J, McKay L, et al. Morphological and functional reversal of phenotypes in a mouse model of Rett syndrome. Brain. Sep 2012; 135(Pt 9): 2699-710. PMID 22525157
7. Suter B, Treadwell-Deering D, Zoghbi HY, et al. Brief report: MECP2 mutations in people without Rett syndrome. J Autism Dev Disord. Mar 2014; 44(3): 703-11. PMID 23921973
8. Cuddapah VA, Pillai RB, Shekar KV, et al. Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome. J Med Genet. Mar 2014; 51(3): 152-8. PMID 24399845
9. Archer H, Evans J, Leonard H, et al. Correlation between clinical severity in patients with Rett syndrome with a p.R168X or p.T158M MECP2 mutation, and the direction and degree of skewing of X-chromosome inactivation. J Med Genet. Feb 2007; 44(2): 148-52. PMID 16905679
10. Weaving LS, Williamson SL, Bennetts B, et al. Effects of MECP2 mutation type, location and X-inactivation in modulating Rett syndrome phenotype. Am J Med Genet A. Apr 15 2003; 118A(2): 103-14. PMID 12655490
11. Liyanage VR, Rastegar M. Rett syndrome and MeCP2. Neuromolecular Med. Jun 2014; 16(2): 231-64. PMID 24615633

12. Zahorakova D, Lelkova P, Gregor V, et al. MECP2 mutations in Czech patients with Rett syndrome and Rett-like phenotypes: novel mutations, genotype-phenotype correlations and validation of high-resolution melting analysis for mutation scanning. J Hum Genet. Jul 2016; 61(7): 617-25. PMID 26984561
13. Sheikh TI, Ausi J, Faghfoury H, et al. From Function to Phenotype: Impaired DNA Binding and Clustering Correlates with Clinical Severity in Males with Missense Mutations in MECP2. Sci Rep. Dec 08 2016; 6: 38590. PMID 27929079
14. Schnewolf-Greulich B, Tejada MI, Stephens K, et al. The MECP2 variant c.925C T (p.Arg309Trp) causes intellectual disability in both males and females without classic features of Rett syndrome. Clin Genet. Jun 2016; 89(6): 733-8. PMID 26936630
15. Huppke P, Laccone F, Krmer N, et al. Rett syndrome: analysis of MECP2 and clinical characterization of 31 patients. Hum Mol Genet. May 22 2000; 9(9): 1369-75. PMID 10814718
16. Cheadle JP, Gill H, Fleming N, et al. Long-read sequence analysis of the MECP2 gene in Rett syndrome patients: correlation of disease severity with mutation type and location. Hum Mol Genet. Apr 12 2000; 9(7): 1119-29. PMID 10767337
17. Bao X, Downs J, Wong K, et al. Using a large international sample to investigate epilepsy in Rett syndrome. Dev Med Child Neurol. Jun 2013; 55(6): 553-8. PMID 23421866
18. Bebbington A, Downs J, Percy A, et al. The phenotype associated with a large deletion on MECP2. Eur J Hum Genet. Sep 2012; 20(9): 921-7. PMID 22473088
19. Lane JB, Lee HS, Smith LW, et al. Clinical severity and quality of life in children and adolescents with Rett syndrome. Neurology. Nov 15 2011; 77(20): 1812-8. PMID 22013176
20. Fabio RA, Colombo B, Russo S, et al. Recent insights into genotype-phenotype relationships in patients with Rett syndrome using a fine grain scale. Res Dev Disabil. Nov 2014; 35(11): 2976-86. PMID 25124696
21. Halbach N, Smeets EE, Julu P, et al. Neurophysiology versus clinical genetics in Rett syndrome: A multicenter study. Am J Med Genet A. Sep 2016; 170(9): 2301-9. PMID 27354166
22. Pidcock FS, Salorio C, Bibat G, et al. Functional outcomes in Rett syndrome. Brain Dev. Jan 2016; 38(1): 76-81. PMID 26175308
23. Sajan SA, Jhangiani SN, Muzny DM, et al. Enrichment of mutations in chromatin regulators in people with Rett syndrome lacking mutations in MECP2. Genet Med. Jan 2017; 19(1): 13-19. PMID 27171548
24. Vidal S, Brandi N, Pacheco P, et al. The utility of Next Generation Sequencing for molecular diagnostics in Rett syndrome. Sci Rep. Sep 25 2017; 7(1): 12288. PMID 28947817
25. Zhang Q, Zhao Y, Bao X, et al. Familial cases and male cases with MECP2 mutations. Am J Med Genet B Neuropsychiatr Genet. Jun 2017; 174(4): 451-457. PMID 28394482
26. Amir RE, Sutton VR, Van den Veyver IB. Newborn screening and prenatal diagnosis for Rett syndrome: implications for therapy. J Child Neurol. Sep 2005; 20(9): 779-83. PMID 16225835
27. Michelson DJ, Shevell MI, Sherr EH, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. Oct 25 2011; 77(17): 1629-35. PMID 21956720
28. Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. Pediatrics. Nov 2007; 120(5): 1183-215. PMID 17967920
29. AAP Publications Retired and Reaffirmed. Pediatrics. Dec 2014;134(5):e1520.
30. Hyman SL, Levy SE, Myers SM, et al. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. Pediatrics. Jan 2020; 145(1). PMID 31843864
31. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med. May 2013; 15(5): 399-407. PMID 23519317

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2012	New policy	
December 2013	Replace policy	Policy updated with literature search, references 3-6, 10, and 11 added. Policy statements unchanged
December 2014	Replace policy	Policy updated with literature search adding references 6, 8-11, 17, and 19 -22. No change to policy statements
June 2017	Replace policy	Policy updated with literature review through March 23, 2017; references 12-14, and 21-23. The policy is revised with updated genetics nomenclature. "Mutations, changed to "variants, in policy statements. Policy statements updated to define "genetic testing for Rett-syndrome associated genes (eg, MECP2, FOXG1 or CDKL5),; Removed "female, requirement of child for testing; Added two new medical necessity statements for "targeted genetic testing for a known familial variant, in a sister of a child with Rett syndrome or a female with a child with Rett syndrome
September 2018	Replace policy	Policy updated with literature review through April 5, 2018; references 23-24 added. Policy statements for "targeted genetic testing for a known familial variant, in a sister of a child with Rett syndrome or a female with a child with Rett syndrome removed as not in the scope of review of this policy due to current FEP benefit limitation for testing of asymptomatic individuals.
September 2019	Replace policy	Policy updated with literature review through March 4, 2019; no references added. Policy statements unchanged.
September 2020	Replace policy	Policy updated with literature review through March 9, 2020; no references added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through February 11, 2021; reference added. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through February 14, 2022; no references added. Minor editorial refinements to policy statements; intent unchanged.
September 2023	Replace policy	Policy updated with literature review through March 27, 2023; reference added. Policy statements unchanged.