MEDICAL POLICY – 12.04.81
Genetic Testing for Rett Syndrome

BCBSA Ref. Policy: 2.04.81
Effective Date: Aug. 1, 2017
Last Revised: July 18, 2017
Replaces: 2.04.81
RELATED MEDICAL POLICIES:
12.04.514 Genetic Testing for Epilepsy

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Rett syndrome is a rare disorder of the nervous system that affects mostly girls. This disorder influences how the brain develops. A girl with Rett syndrome grows normally for about the first six to eighteen months. Then, noticeable changes develop. The child's loses the muscle ability she had already developed, so activities like crawling, walking, or using the hands begin to diminish. (Some boys also develop Rett syndrome but because of their chromosomal makeup they die before birth or as early in infancy.) A genetic change (mutation) is responsible for Rett syndrome. But this genetic change usually isn’t inherited from a parent. It most often occurs by chance. Rett syndrome can’t be cured. However, treatments can be used to help manage symptoms and provide support. Such care is usually needed throughout life. A genetic test is available to see if a person has Rett syndrome. This policy describes when the genetic test may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
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</table>
| Genetic testing for Rett syndrome | Genetic testing for Rett syndrome –associated genes (eg, MECP2, FOXG1, or CDKL5) may be considered medically necessary when the following criteria are met:  
  • To establish a genetic diagnosis of Rett syndrome in a child with developmental delay and signs/symptoms of Rett syndrome |
| Targeted genetic testing for a known familial Rett syndrome–associated variant | Testing for that variant is medically necessary to determine carrier status of a mother or a sister of an individual with Rett syndrome. |

<table>
<thead>
<tr>
<th>Service</th>
<th>Investigational</th>
</tr>
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</table>
| All other indications for genetic testing for Rett syndrome–associated genes | All other indications for genetic testing for Rett syndrome - associated genes (eg, MECP2, FOXG1, or CDKL5) are considered investigational including:  
  • Carrier testing (preconception or prenatal) in the absence of a family history of Rett’s disease.  
**AND**  
  • Testing of asymptomatic family members to determine future risk of the disease. |

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
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<tr>
<td>81302</td>
<td>MECP2 (methyl CpG binding protein 2)(eg, Rett syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81303</td>
<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81304</td>
<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<td>-----------------------------------------------------------------------------</td>
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<tr>
<td></td>
<td>characterization of a dynamic mutation disorder/triplet repeat by Southern</td>
</tr>
<tr>
<td></td>
<td>blot analysis)</td>
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<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA</td>
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<td>sequence analysis, mutation scanning or duplication/deletion variants of 26-</td>
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<td></td>
<td>50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
</tbody>
</table>

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**Related Information**

**Genetic Counseling**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Evidence Review**

**Description**

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 a patient with clinical features of RTT or in an RTT patient’s family member.
Background

**Rett syndrome**

Rett syndrome (RTT) is a severe neurodevelopmental disorder primarily affecting girls. It occurs in 1 out of every 10,000 female births, making it among the most common genetic causes of intellectual disability in girls. Girls with RTT have what seems to be normal development for the first 6 to 18 months of life, followed by regression of acquired fine and gross motor skills, intellectual functioning, and social skills. Purposeful use of the hands is replaced by repetitive stereotypical hand movements, such 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 may also be more severe or milder variants. The severe variant has no normal developmental period, while individuals with a mild form have less dramatic regression of their initial abilities and milder expression of the characteristics of classical RTT. Diagnostic criteria for typical (or classic) RTT and atypical (or variant) RTT have been established.

**Treatment**

Currently, there are no specific treatments that halt or reverse disease progression, 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 applied, with input from dietitians, physical therapists, occupational therapists, speech therapists, and music therapists. Regular monitoring for scoliosis (seen in ≈87% of RTT patients by age 25 years) and possible heart abnormalities, particularly cardiac conduction abnormalities, may be recommended. Spasticity can have a major impact on mobility, and physical therapy and hydrotherapy may prolong mobility. Occupational therapy can help children develop communication strategies and skills needed for performing self-directed activities (eg, dressing, feeding, practicing arts and crafts).

Pharmacologic approaches to managing problems associated with RTT include melatonin for sleep disturbances and several agents to control 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 certain drugs is recommended, including prokinetic agents, antipsychotics, tricyclic antidepressants, antiarrhythmics, anesthetic agents, and certain antibiotics.
In a mouse model of RTT, genetic manipulation of the MECP2 gene has demonstrated reversibility of the genetic defect.\textsuperscript{4,5}

**Genetics of RTT**

RTT is an X-linked dominant genetic disorder. Pathogenic variants in MECP2, which is thought to control expression of several genes including some involved in brain development, were first reported in 1999. Subsequent screening has shown that over 80\% of patients with classic RTT have at least one of 200+ pathogenic variants in the MECP2 gene.\textsuperscript{6} However, 8 of the most commonly occurring missense and nonsense variants account for almost 70\% of all cases. Small C-terminal deletions account for approximately 10\%, while large deletions are responsible for 8\% to 10\%.\textsuperscript{7} The specific type of MECP2 variant is associated with disease severity.\textsuperscript{8} 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. Additionally, the pattern of X-chromosome inactivation influences the severity of the clinical disease in females.\textsuperscript{9,10}

Because there is a broad spectrum of clinical phenotypes, in order to facilitate genotype-phenotype correlation analyses the 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 and result almost exclusively from a de novo variant on the paternally derived X chromosome. The remaining 0.5\% of cases are familial, usually caused by germline mosaicism or favorably skewed X-chromosome inactivation in a carrier mother. These carrier mothers are usually unaffected or only slightly affected (mild intellectual disability). In the case of a carrier mother, the recurrence risk of having RTT in another child is 50\%. If a variant is not identified in the mother’s leukocytes, the risk to a sibling of the proband is below 0.5\% (because germline mosaicism in either parent cannot be excluded).

Having a variant in the MECP2 gene does not necessarily mean the person has 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.\textsuperscript{1,6,11} Recent studies have revealed that different classes of genetic variants in MECP2 result in variable clinical phenotypes and overlap with other neurodevelopmental disorders.\textsuperscript{12-14}
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, FOXG1) have been shown to be associated with atypical variants.

**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 to establish a specific genetic diagnosis has clinical utility when signs and symptoms of RTT are present. 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.

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, 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 a meaningful improvement in the net health outcome.

For female individuals who have a child with RTT and are considering having another child, the evidence for targeted genetic testing for a known familial RTT-associated variant includes cases series and prospective cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, and changes in reproductive decision making. Such genetic testing may help with 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 a meaningful improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**

Some trials that might influence this policy are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><strong>Ongoing</strong></td>
<td></td>
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<tr>
<td><strong>NCT01520363</strong></td>
<td>Placebo Controlled Trial of Dextromethorphan in Rett Syndrome</td>
<td>60</td>
<td>Dec 2017</td>
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<tr>
<td><strong>NCT02061137</strong></td>
<td>A Phase 1 Clinical Study to Assess Safety and Efficacy of Oral Fingolimod (FTY720) in Children With Rett Syndrome.</td>
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<td>Jul 2018</td>
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<tr>
<td><strong>NCT02171104</strong></td>
<td>MT2013-31: Allogeneic Hematopoietic Cell Transplantation for Inherited Metabolic Disorders and Severe Osteopetrosis Following Conditioning With Busulfan (Therapeutic Drug Monitoring), Fludarabine +/- ATG</td>
<td>100</td>
<td>Sep 2019</td>
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<td></td>
<td><strong>Unpublished</strong></td>
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<tr>
<td><strong>NCT00990691</strong></td>
<td>Pilot Study of the Effects of the Desipramine on the Neurovegetative Parameters of the Child With Rett Syndrome</td>
<td>36</td>
<td>Dec 2014 (completed)</td>
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<tr>
<td><strong>NCT02023424</strong></td>
<td>An Open Label, Exploratory Study to Investigate the Treatment Effect of Glatiramer Acetate (Copaxone ®) on Girls With Rett Syndrome</td>
<td>10</td>
<td>Feb 2015 (unknown)</td>
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<tr>
<td><strong>NCT02153723</strong></td>
<td>Pharmacological Treatment of Rett Syndrome With Glatiramer Acetate (Copaxone)</td>
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<td>Jun 2015 (unknown)</td>
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<td><strong>NCT01777542</strong></td>
<td>Pharmacological Treatment of Rett Syndrome by Stimulation of Synaptic Maturation With Recombinant Human IGF-1(Mecasermin [rDNA] Injection)</td>
<td>30</td>
<td>Nov 2016 (completed)</td>
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</table>

NCT: national clinical trial.
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests while this policy was under review in 2012, input on the use variant testing for Rett syndrome (RTT) was received from 2 specialty medical societies (3 reviewers) and 3 academic medical centers, for a total of 6 reviewers. There was consensus or near consensus supporting the use of variant testing for the diagnosis of RTT in a girl in whom the clinical differential diagnosis includes RTT, especially when clinical diagnosis is uncertain. Support for testing sisters of individuals with RTT and for prenatal screening was mixed.

Practice Guidelines and Position Statements

American Academy of Neurology/Child Neurology Society

In 2011, the American Academy of Neurology (AAN) and the Child Neurology Society (CNS) issued an evidence report on genetic and metabolic testing of children with global developmental delay.\(^{25}\) AAN and CNS recommended considering methyl-CpG-binding protein 2 (MECP2) genetic testing for all girls with unexplained moderate-to-severe developmental delay.

American Academy of Pediatrics

A 2007 policy statement\(^{26}\) from the American Academy of Pediatrics (AAP; reaffirmed in 2010\(^{27}\)) recommended MECP2 testing to confirm a diagnosis of suspected Rett syndrome (RTT), especially when the diagnosis was unclear from symptoms alone.

RettSearch International Consortium of Rett Syndrome Clinical Researchers

Neither AAN nor AAP has provided recommendations on when to use CDKL5 or FOXG1 testing. In 2010, RettSearch, a consortium of international clinical RTT specialists, suggested that patients...
who are negative for MECP2 variants and have a strong clinical diagnosis of RTT 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 (eg, severe postnatal microcephaly).³

**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.²⁸ 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 autistic spectrum disorders was not recommended.

**Medicare National Coverage**

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

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

**References**


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/11/12</td>
<td>New policy. Policy statements state that 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.</td>
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<tr>
<td>01/14/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
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<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
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<tr>
<td>12/04/13</td>
<td>Replace Policy. Policy updated with a literature search through July 2013; references 3-6, 10 and 11 added. Policy statements unchanged. CPT codes 81404 and 81406 added as new codes specific to this policy.</td>
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<td>01/03/14</td>
<td>Update Related Policies; add 12.04.109, effective 12/9/13.</td>
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<tr>
<td>11/20/14</td>
<td>Annual Review. Policy updated with literature review through August 18, 2014; references 6, 8-11, 17, 19-22 added; reference 12 updated; others renumbered/removed. Policy statements unchanged.</td>
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<td>06/16/15</td>
<td>Update Related Policies. 12.04.109 renumbered to 12.04.514.</td>
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<tr>
<td>12/08/15</td>
<td>Annual Review. Policy updated with literature review through October 31, 2015; no references added. Policy statement edited for clarity, no change to intent of policy statement.</td>
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<tr>
<td>12/01/16</td>
<td>Annual review, approved November 8, 2016. Review. Policy updated with literature review through September 2016; references added. Policy statement unchanged,</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
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<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>08/01/17</td>
<td>Annual review, approved July 18, 2017. Policy moved into new format. Policy updated with literature review through March 23, 2017; references 12-14 and 21-23. The policy is revised with updated genetics nomenclature. &quot;Mutations&quot; changed to &quot;variants&quot; in policy statements. Policy rewritten limit populations to sisters of child with Rett syndrome (indication 2) or females with a child with Rett syndrome (indication 3) and revised to &quot;targeted genetic testing for a known familial variant.&quot; Policy statements updated to define &quot;genetic testing for Rett syndrome– associated genes (eg, MECP2, FOXG1, or CDKL5)&quot;; Removed “female” requirement of child for testing; Added 2 new medical necessity statements for “targeted genetic testing for a known familial variant” in a sister or mother of a child with Rett syndrome.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

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  • Information written in other languages

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Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

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You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at: https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Français (French):

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Avi sila a gen enfòmasyon enpòtan ladanann. Avi sila a kapab genyen enfòmasyon enpòtan konsènplan aplikasyon yon lwa osa konsènan kouvètis asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka kente kouvètis asirans sante w la osa pou yo ko ede w avèk defans yo. Se dwa w pou resewa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):

Iloko (Ilocano):
Daytoy a Pakdaak ket naglaon iti Napategy nipa Impomarsa. Daytoy a pakdaak mabalins nga adda ket naglaon iti napategy nga impomarsa maipaggeen iti aplikasyonowo yenyen coverage babaen iti Premera Blue Cross. Daytoy ket mabalins dagiti importante a pelsa iti daytoy a pakdaak. Mabalins nga adda rumbenga nga aramidenyo nga addaagency dagiti partikular a naituding nga laoyan nga tapo tapo napagatimadlyo ti coverage ti saluyawo yenyen tungol kadagiti gastos. Adda karbengano a mangala iti daytoy nga impomarsa ken tungol ti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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Premera Blue Cross (English):
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Tajalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay nagagamit para sa use sa solicitude o cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es posible que deba tornar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Vietnamese (Vietnamese):