MEDICAL POLICY – 12.04.88
Genetic Testing for PTEN Hamartoma Tumor Syndrome

BCBSA Ref. Policy: 2.04.88
Effective Date: May 1, 2018
Last Revised: April 3, 2018
Replaces: 2.04.88

Related Medical Policies:
12.04.93 Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

Select a hyperlink below to be directed to that section.

Policy Criteria | Coding | Related Information
Evidence Review | References | History

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Introduction

PTEN is a gene on one of our chromosomes. If there are abnormal changes in this gene (variants), it may cause “PTEN hamartoma tumor syndrome” (PHTS). PHTS is a condition in which benign (non-cancerous) tumor-like growths called hamartomas grow throughout the body. Even though the hamartomas that grow because of PHTS are not cancer, some types of PHTS can lead to actual cancers developing in the body.

Genetic testing to look for mutations in the PTEN gene may be needed in order to confirm the diagnosis of PTEN hamartoma tumor syndrome. This policy describes when this genetic testing may be 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
Testing Medical Necessity

<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing for PTEN</td>
<td>Genetic testing for PTEN may be considered medically necessary to confirm the diagnosis when a patient has clinical signs of a PTEN hamartoma tumor syndrome.</td>
</tr>
</tbody>
</table>
| Targeted genetic testing for a PTEN familial variant | Targeted genetic testing for a PTEN familial variant may be considered medically necessary in a first-degree relative* of a proband with a known PTEN pathogenic variant.  

Genetic testing for PTEN is considered investigational for all other indications.

| Note:           | *Please refer to the Definition of Terms for additional information about terms and acronyms used in this policy. |

Testing a First-Degree Relative

When a PTEN disease-associated variant is identified in the proband, testing of asymptomatic at-risk relatives can identify those family members who also carry the familial variant, for whom initial evaluation and ongoing surveillance should be performed.

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81321</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis</td>
</tr>
</tbody>
</table>

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Related Information
**Definition of Terms**

**Close blood relatives - degrees of relationship:** close blood relatives are on the same side of the family, either maternal (mother) or paternal (father). The maternal and paternal sides of the family should be considered independently for familial patterns of inheritance.

<table>
<thead>
<tr>
<th>Degree</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Degree</td>
<td>Parents, siblings (brother/sister), and children</td>
</tr>
<tr>
<td>2nd Degree</td>
<td>Grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (brother/sister)</td>
</tr>
<tr>
<td>3rd Degree</td>
<td>Great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins</td>
</tr>
</tbody>
</table>

**Penetrance:** The proportion of individuals with a variant that causes a particular disorder/disease who exhibit clinical symptoms.

**Proband:** The first affected individual in a family who brings a genetic disorder to the attention of the medical community (sometimes also known as the index patient).

**Definition of Acronyms**

- **BRRS:** Bannayan-Riley-Ruvalcaba syndrome
- **CS:** Cowden syndrome
- **LDD:** Lhermitte-Duclos disease
- **PHTS:** PTEN hamartoma tumor syndrome
- **PLS:** Proteus-like syndrome
- **PS:** PTEN-related Proteus syndrome
- **PTEN:** Phosphatase and tensin homologue, a gene found on chromosome 10

**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 (see Table 1).
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 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

<table>
<thead>
<tr>
<th>Table 1. Nomenclature to Report on Variants Found in DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous</strong></td>
</tr>
<tr>
<td>Mutation</td>
</tr>
<tr>
<td>Variant</td>
</tr>
<tr>
<td>Familial variant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. ACMG-AMP Standards and Guidelines for Variant Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variant Classification</strong></td>
</tr>
<tr>
<td>Pathogenic</td>
</tr>
<tr>
<td>Likely pathogenic</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
</tr>
<tr>
<td>Likely benign</td>
</tr>
<tr>
<td>Benign</td>
</tr>
</tbody>
</table>

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 the understanding of 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.

Evidence Review

Description

The PTEN hamartoma tumor syndrome (PHTS) includes several syndromes with heterogeneous clinical symptoms, which may place individuals at an increased risk for the development of certain types of cancer. Genetic testing for PTEN can confirm a diagnosis of PHTS.

Background

PTEN Hamartoma Tumor Syndromes

PTEN hamartoma tumor syndrome (PHTS) is characterized by hamartomatous tumors and PTEN germline disease-associated variants. Clinically, PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome (PLS).

CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules and present by age late 20s. The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer, usually follicular carcinoma, is approximately 35%. The risk for endometrial cancer is not well-defined, but may approach 28%. A 2012 study included 3399 prospectively recruited individuals who met relaxed International Cowden Consortium PHTS criteria; 368 were found to have PTEN disease-associated variants. Estimated lifetime cancer risks were:

- 85.2% for breast (95% confidence interval [CI], 71.4% to 99.1%)
- 35.2% for thyroid (95% CI, 19.7% to 50.7%)
- 28.2% for endometrium (95% CI, 17.1% to 39.3%)
- 9.0% for colorectal (95% CI, 3.8% to 14.1%)
- 33.6% for kidney (95% CI, 10.4% to 56.9%)
- 6% for melanoma (95% CI, 1.6% to 9.4%)

A 2013 study of 154 individuals with a PTEN disease-associated variant found cumulative risk for any cancer at age 70 of 85% (95% CI, 70% to 95%) for any cancer, 77% (95% CI, 59% to 91%) for female breast cancer, and 38% (95% CI, 25% to 56%) for thyroid cancer.³

BRRS is characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis. Additional features include high birth weight, developmental delay and mental deficiency (50% of affected individuals), a myopathic process in proximal muscles (60%), joint hyperextensibility, pectus excavatum, and scoliosis (50%).

PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

PLS is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

CS is the only PHTS disorder associated with a documented predisposition to cancer; however, it has been suggested that patients with other PHTS diagnoses associated with PTEN variants should be assumed to have cancer risks similar to CS.

**Clinical Diagnosis**

A presumptive diagnosis of PHTS is based on clinical findings; however, because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a PTEN disease-associated variant is identified.

**Diagnostic Criteria for Cowden Syndrome**

The International Cowden Consortium has developed criteria for diagnosing CS (see Table 3).⁴
Table 3. Diagnostic Criteria for Cowden Syndrome

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Pathognomonic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lhermitte-Duclos disease adult defined as the presence of a cerebellar dysplastic gangliocytoma</td>
</tr>
<tr>
<td></td>
<td>• Mucocutaneous lesions:</td>
</tr>
<tr>
<td></td>
<td>o Trichilemmomas, facial</td>
</tr>
<tr>
<td></td>
<td>o Acral keratoses</td>
</tr>
<tr>
<td></td>
<td>o Papillomatous lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Breast cancer</td>
</tr>
<tr>
<td></td>
<td>• Thyroid cancer (papillary or follicular)</td>
</tr>
<tr>
<td></td>
<td>• Macrocephaly (occipital frontal circumference ≥ 97th percentile)</td>
</tr>
<tr>
<td></td>
<td>• Endometrial cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Other structural thyroid lesions (eg, adenoma, multinodular goiter)</td>
</tr>
<tr>
<td></td>
<td>• Mental retardation (ie, IQ ≤ 75)</td>
</tr>
<tr>
<td></td>
<td>• Gastrointestinal hamartomas</td>
</tr>
<tr>
<td></td>
<td>• Fibrocystic disease of the breast</td>
</tr>
<tr>
<td></td>
<td>• Lipomas</td>
</tr>
<tr>
<td></td>
<td>• Fibromas</td>
</tr>
<tr>
<td></td>
<td>• Genitourinary tumors (eg, uterine fibroids, renal cell carcinoma) or</td>
</tr>
<tr>
<td></td>
<td>• Genitourinary structural malformations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Operational diagnosis in an individual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any of the following:</td>
</tr>
<tr>
<td></td>
<td>• Mucocutaneous lesions alone if:</td>
</tr>
<tr>
<td></td>
<td>o There are 6 or more facial papules, of which 3 or more must be trichilemmoma, or</td>
</tr>
<tr>
<td></td>
<td>o Cutaneous facial papules and oral mucosal papillomatosis, or</td>
</tr>
<tr>
<td></td>
<td>o Oral mucosal papillomatosis and acral keratoses, or</td>
</tr>
<tr>
<td></td>
<td>o Palmoplantar keratoses, 6 or more</td>
</tr>
<tr>
<td></td>
<td>• Two or more major criteria, but one must include macrocephaly or Lhermitte-Duclos disease; or</td>
</tr>
<tr>
<td></td>
<td>• One major and 3 minor criteria; or</td>
</tr>
<tr>
<td></td>
<td>• Four minor criteria.</td>
</tr>
</tbody>
</table>
Diagnostic Criteria

Operational diagnosis in a family with a diagnosis of Cowden syndrome

- One pathognomonic criterion; or
- Any 1 major criterion with or without minor criteria; or
- Two minor criteria; or
- History of Bannayan-Riley-Ruvalcaba syndrome

Adapted from Blumenthal et al (2008).^4

^ These criteria for diagnosing Cowden syndrome have been adopted by the National Comprehensive Cancer Network.

In 2013, a systematic review assessed the clinical features reported in individuals with a PTEN disease-associated variant, and proposed revised diagnostic criteria. Reviewers concluded that there was insufficient evidence to support inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. There was sufficient evidence to include autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis, and vascular anomalies, and these clinical features are included in CS testing minor criteria in the National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment of breast and ovarian cancer (v.2.2018).^6

**Bannayan-Riley-Ruvalcaba Syndrome**

Diagnostic criteria for BRRS have not been set. Current diagnostic practices are based heavily on the presence of the cardinal features of macrocephaly, hamartomatous intestinal polyposis, lipomas, and pigmented macules of the glans penis.

**Proteus Syndrome**

PS appears to affect individuals in a mosaic distribution (ie, only some organs/tissues are affected). Thus, it is frequently misdiagnosed, despite the development of consensus diagnostic criteria. Mandatory general criteria for diagnosis include mosaic distribution of lesions, progressive course, and sporadic occurrence. Additional specific criteria for diagnosis as listed in Table 4.^7
### Table 4. Diagnostic Criteria for Proteus Syndrome

#### Additional Diagnostic Criteria

- Connective tissue nevi (pathognomonic)

  OR

- Two of the following:
  - Epidermal nevus
  - Disproportionate overgrowth (1 or more)
    - Limbs: arms/legs; hands/feet/digits
    - Skull: hyperostoses
    - External auditory meatus: hyperostosis
    - Vertebrae: megaspondylo dysplasia
    - Viscera: spleen, thymus
  - Specific tumors before the end of the second decade (either one):
    - Bilateral ovarian cystadenoma
    - Parotid monomorphic adenoma

  OR

- Three of the following:
  - Dysregulated adipose tissue (either lipomas or regional absence of fat)
  - Vascular malformations (1 or more):
    - Capillary malformation
    - Venous malformation
    - Lymphatic malformation
  - Facial phenotype:
    - Dolichocephaly
    - Long face
    - Minor downsloping of palpebral fissures and/or minor ptosis
    - Low nasal bridge
    - Wide or anteverted nares
    - Open mouth at rest

Adapted from Biesecker (2006).
**Proteus-like Syndrome**

PLS is undefined but describes individuals with significant clinical features of PS but who do not meet the diagnostic criteria.

**Molecular Diagnosis**

PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a tumor suppressor gene on chromosome 10q23 and is dual specificity phosphatase with multiple but incompletely understood roles in cellular regulation. PTEN disease-associated variants are inherited in an autosomal dominant manner.

Most CS cases are simplex. However, because CS is likely underdiagnosed, the actual proportion of simplex cases (ie, individuals with no obvious family history) and familial cases (ie, ≥2 related affected individuals) cannot be determined. It is estimated that 50% to 90% of cases of CS are de novo and approximately 10% to 50% of individuals with CS have an affected parent.

Because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a PTEN disease-associated variant is identified. Up to 85% of patients who meet the clinical criteria for a diagnosis of CS and 65% of patients with a clinical diagnosis of BRRS have a detectable PTEN disease-associated variant. Some data have suggested that up to 20% of patients with PS and up to 50% of patients with a PLS have PTEN disease-associated variants.

Most of these mutations can be identified by sequence analysis of the coding and flanking intronic regions of genomic DNA. A smaller number of mutations are detected by deletion/duplication or promoter region analysis.

**Penetrance**

More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s. By the third decade, 99% of affected individuals develop the mucocutaneous stigmata, primarily trichilemmomas and papillomatous papules, as well as acral and plantar keratoses.
Management

Treatment

Treatment of the benign and malignant manifestations of PHTS is the same as for their sporadic counterparts (ie, chemotherapy, surgery, and/or radiotherapy as per usual guidelines and clinical practice).

Surveillance

The most serious consequences of PHTS relate to the increased risk of cancers, including breast, thyroid, and endometrial, and to a lesser extent, renal. Therefore, the most important aspect of management of an individual with a PTEN disease-associated variant is increased cancer surveillance to detect tumors at the earliest, most treatable stages.

Summary of Evidence

For individuals who have clinical signs and/or symptoms of PHTS or who are asymptomatic with a first-degree relative with a PHTS and a known familial variant who receive genetic testing for a PTEN familial variant, the evidence includes case series and a large prospective study on the frequency of a PTEN variants in individuals meeting clinical criteria for a PHTS, and studies of cancer risk estimates in individuals with a PTEN disease-associated variant. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and morbid events. The published clinical validity of testing for the PTEN gene is variable. The true clinical validity is difficult to ascertain, because the syndrome is defined by the presence of a PTEN disease-associated variant. The sensitivity of tests for CS and BRRS has been reported to be up to 80% and 60%, respectively. Direct evidence of the clinical utility of genetic testing for PTEN is lacking; however, confirming a diagnosis in a patient with clinical signs of a PHTS will lead to changes in clinical management by increasing surveillance to detect cancers associated with PHTS at an early and treatable stage. Although most cases of a PHTS occur in individuals with no known family history of PHTS, testing of at-risk relatives will identify those who should also undergo increased cancer surveillance. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in January 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

Practice Guidelines and Position Statements

Current National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v.2.2018) recommend the following for Cowden syndrome management (see Table 5).

Table 5. Guidelines on Genetic/Familial High-Risk Assessment for Breast and Ovarian Cancer

<table>
<thead>
<tr>
<th>Populations</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Women       | • Breast awareness starting at age 18 years.  
              • Clinical breast exam every 6 to 12 months, starting at age 25 years or 5 to 10 years before the earliest known breast cancer in the family (whichever comes first).  
              • Breast screening:  
                  o Annual mammography and breast MRI screening starting at age 30 to 35 years or 5 to 10 years before the earliest known breast cancer in family (whichever comes first).  
                  o Age >75, management should be considered on an individual basis.  
              • For women with a PTEN mutation [disease-associated variant] who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.  
              • For endometrial cancer screening, encourage patient education and prompt response to symptoms. Consider annual random endometrial biopsies and/or ultrasound beginning at age 30 to 35 years.  
              • Discuss risk-reducing mastectomy and hysterectomy and counsel regarding degree of protection, extent of cancer risk, and reconstructive options. |
| Men and women | • Annual comprehensive physical exam starting at age 18 years or 5 years before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to breast and thyroid exam.  
                • Annual thyroid ultrasound starting at the time of PHTS diagnosis.  
                • Colonoscopy, starting at age 35 years, unless symptomatic or a close relative with colon cancer under age 40 years. Colonoscopy should be done every 5 years or more frequently if... |
Populations | Recommendations
---|---
| patient is symptomatic or polyps found.
- Dermatologic management may be indicated for some patients.
- Consider renal ultrasound starting at age 40 years, then every 1 to 2 years.
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms
- Education regarding signs and symptoms of cancer

Relatives | 
- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives

Reproductive options | 
- For women of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including preimplantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies

MRI: magnetic resonance imaging; PHTS: PTEN hamartoma tumor syndrome.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for genetic testing for PTEN hamartoma tumor syndrome have been identified.

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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratory testing for PTEN variants is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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>04/08/13</td>
<td>New Policy. Policy created with literature search through January 2013. Medically necessary to confirm a diagnosis in a patient with signs of PHTS and in first degree relatives of a proband with a known PTEN mutation. Genetic testing for a PTEN mutation is considered investigational for all other indications, including, but not</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<tr>
<td>limited to, prenatal testing.</td>
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<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>05/05/14</td>
<td>Annual Review. Policy updated with literature search through January 9, 2014; reference 1 added. Prenatal testing removed from the investigational statement. Clarification of testing strategy in Policy Guidelines.</td>
</tr>
<tr>
<td>05/01/16</td>
<td>Annual Review, approved April 12, 2016. Policy updated with literature review through December 18, 2015; references 1-3 added. Added Definition of Terms to Guidelines section. Added Categories of Genetic Testing to Appendix. Policy statements unchanged.</td>
</tr>
<tr>
<td>05/01/17</td>
<td>Annual Review, approved April 11, 2017. Policy updated with literature review through January 11, 2017; no references added. The policy is revised with updated genetics nomenclature - mutation changed to variant. The appendix table is removed with the categories of genetic testing addressed in the policy included in the opening narrative of the Rationale section. Coding update; removed CPT codes 81322 and 81323. Policy statements unchanged.</td>
</tr>
<tr>
<td>09/22/17</td>
<td>Policy moved to new format. No changes to policy statements.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through December 2017; no references added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Deutsche (German):

Hmoob (Hmong):

Illoko (Ilocano):
Daytoy a Pakdaa ket naglaon iti Napateg nga Impormason. Daytoy a pakdaa mabal bin nga adda ket naglaon iti napateg nga impormasjon maipanggepp iti aplanisyon weno coverage babaen iti Premera Blue Cross. Daytoy ket mabalbin dagiti importante a pelsa iti daytoy a pakdaar. Mabalbin nga adda rumbeng nga aramindeng nga adda sabbay dagiti particular a naituding nga alaw napo tmapalagginadyo ti coverage ti salun-atyo weno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasjon ken tulong ti bukodyo a pagasasao nga awan tibayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.
Chiamata 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):
本通知有重要的讯息。本通知可能有关於您透过 Premera Blue Cross 提交的申请或保险的重要讯息。本通知内可能有重要日期。您可能需要在截止日期之前採取行动，以保留您的健康保险或费用补贴。您有权利免费以您的母语得到本讯息和帮助。请拨电话 800-722-1471 (TTY: 800-842-5357)。
預報通知

這一通知包含了重要的信息。此通知由Premera Blue Cross發送，可能會對您的保單產生影響。請仔細閱讀此通知，並按照指示操作。如有任何問題，請致電800-722-1471 (TTY: 800-842-5357)。

この通知には重要な情報が含まれています。この通知はPremera Blue Crossから出され、あなたの保険の影響を及ぼす可能性があります。この通知を細かく読んでください。問題がある場合は、800-722-1471 (TTY: 800-842-5357) へお問い合わせください。

Предупреждение

В данном уведомлении указаны важные сведения. Это уведомление было отправлено Premera Blue Cross и может повлиять на ваши условия страхования. Пожалуйста, внимательно прочтите это уведомление, и в случае вопросов звоните 800-722-1471 (TTY: 800-842-5357).


Русский (Russian):

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам необходимо внимательно прочитать все уведомление. Если у вас есть вопросы, вы можете позвонить по телефону 800-722-1471 (TTY: 800-842-5357).

這則通知包含重要信息。這則通知可能影響您的保險。請詳細閱讀此通知，並如您有任何問題，請聯絡800-722-1471 (TTY: 800-842-5357)。


Informação essencial.


 важна информация.

Ця повідомлення містить важливу інформацію. Ця повідомлення може містити інформацію про ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на дату, яка може вказувати на важке обставини. Ви можете звернутися з питаннями до нас шляхом звонку на 800-722-1471 (TTY: 800-842-5357) .