Genetic Testing for Tamoxifen Treatment

Introduction

Certain types of breast cancer are affected by hormones. Cancer cells that are said to be estrogen receptor positive (ER-positive) have receptors that attach to estrogen. Once attached, estrogen then acts like a fertilizer to help the cancer grow. Hormone therapy is used to prevent estrogen from connecting to the receptors. Tamoxifen is a type of hormone therapy that can be used for ER-positive breast cancer to prevent it from coming back and to treat breast cancer that's already spread to other parts of the body. It’s also used for ER-positive ductal carcinoma in situ (DCIS). To process tamoxifen into its more active form, the body uses a specific, important enzyme (CYP2D6) that's made by a particular gene. A small percentage of people (about 10%) have a form of the gene that doesn’t make as much of this important enzyme as most other people make. A genetic test has been developed to try to see if a person has the gene form that makes a smaller amount of the needed enzyme. This genetic test is investigational (unproven). Large, well-designed medical studies don’t show a strong link between this gene and tamoxifen’s effectiveness. More studies are needed.

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

Test | Investigational
---|---
Cytochrome p450 2D6 (CYP2D6) testing | Genotyping to determine cytochrome p450 2D6 (CYP2D6) variants is considered investigational for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer.

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81225</td>
<td>CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)</td>
</tr>
<tr>
<td>81227</td>
<td>CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
</tbody>
</table>

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review
Description

Tamoxifen is prescribed as a component of adjuvant endocrine therapy to prevent estrogen receptor-positive breast cancer recurrence, to treat metastatic ER-positive breast cancer, and to prevent disease in high-risk populations and in women with ductal carcinoma in situ (DCIS). The cytochrome P450 (CYP450) metabolic enzyme, CYP2D6, has a major role in tamoxifen metabolism. Some organizations have recommended that patients who are prescribed tamoxifen be genotyped for CYP2D6, and that patients who are poor metabolizers be treated with alternative therapy, if possible.

Background

Tamoxifen Metabolism

Tamoxifen undergoes extensive primary and secondary metabolism, and plasma concentrations of tamoxifen and its metabolites vary widely. The metabolite 4-hydroxytamoxifen (4-OH tamoxifen) has demonstrated 100-fold greater affinity for the estrogen receptor and 30- to 100-fold greater potency in suppressing estrogen-dependent cell proliferation in vitro compared with the parent drug (summarized in Goetz et al [2008]). Another metabolite, 4-hydroxy-N-desmethyl tamoxifen (endoxifen), has properties and potency identical to 4-OH tamoxifen. Because 4-OH tamoxifen represents less than 20% of the product of tamoxifen primary metabolism, and because steady-state plasma endoxifen concentrations are on average 5- to 10-fold higher than 4-OH tamoxifen plasma levels, it has been assumed that endoxifen is the major active metabolite of tamoxifen.

The metabolism of tamoxifen to 4-OH tamoxifen is catalyzed by multiple enzymes. However, endoxifen is formed predominantly by CYP2D6. Plasma concentrations of endoxifen exhibit high interindividual variability, as described in breast cancer patients. Because CYP2D6 enzyme activity is known to vary across individuals, CYP2D6 is of great interest for understanding tamoxifen metabolism variability and variation in levels of circulating active metabolites. Moreover, known variability in endoxifen levels has been hypothesized to result in variable response to tamoxifen treatment.

Alternatively and more recently, it has been estimated that at doses used for adjuvant treatment, which are intended to saturate the estrogen receptor, more than 99% of estrogen receptors are bound by low-affinity tamoxifen and both low- and high-affinity metabolites. Lash et al (2009)
modeled the effect of CYP2D6 variant alleles on estrogen receptor binding by tamoxifen and metabolites and found negligible effect.⁷ As the authors note, however, modeling cannot account for many metabolic complexities, and mechanistic data would be needed to show how a decrease in high-affinity metabolites associated with CYP2D6 variants reduces the protection against recurrence conferred by tamoxifen therapy.

**Metabolic Enzyme Genotypes**

The CYP2D6 gene exhibits a high degree of polymorphism, with more than 75 allelic variants identified. Although the most prevalent CYP2D6 *1 and *2 alleles (both termed “wild-type” for this policy) produce an enzyme with normal activity, there are several variant alleles that result in enzymes with no activity or reduced activity. Because individuals have 2 CYP2D6 alleles, various combinations of the possible alleles result in a spectrum of CYP2D6 function. These have been categorized as extensive metabolizers (EMs or “normal”), intermediate metabolizers (IMs), and poor metabolizers (PMs). An additional, rare category of ultrarapid metabolizers (UMs) is defined by possession of 3 or more functional alleles due to gene duplication.

The prevalence of CYP2D6 PMs is approximately 7% to 10% in whites of Northern European descent, 1.9% to 7.3% in blacks, and 1% or less in most Asian populations studied. The PM phenotype in whites is largely accounted for by CYP2D6*3 and *4 nonfunctional variants, and in black and Asian populations, by the *5 nonfunctional variant. Some PMs may have 1 nonfunctional allele and 1 reduced function allele. Among reduced function variants, CYP2D6*17, *10, and *8 are the most important in blacks, Asians, and whites, respectively. Few studies have investigated the frequency of CYP2D6 variant alleles or of PMs in the Hispanic population.⁸

Other enzymes metabolize tamoxifen to the active metabolite, 4-OH tamoxifen. Polymorphisms in the genes for these enzymes could have an effect on overall tamoxifen efficacy. Research regarding the effect of variant alleles on these enzymes is in early stages.

**Endocrine Therapy Regimens**

Tamoxifen has several labelled indications⁹:

- Chemoprevention of invasive breast cancer in high-risk women without current disease or with DCIS
- Adjuvant treatment of primary breast cancer
• Treatment of metastatic disease

In women with breast cancer, estrogen receptor-positive disease predicts likely benefit from tamoxifen treatment.

Tamoxifen is currently the most commonly prescribed adjuvant treatment to prevent recurrence of endocrine receptor-positive breast cancer in pre- or peri-menopausal women. The pharmacogenomic evaluation could direct consideration of ovarian ablation or suppression in those found to be CYP2D6 PMs. In pre- or peri-menopausal women with hormone receptor-positive tumors, ovarian ablation is more effective treatment than no adjuvant therapy but may be accompanied by acute and chronic adverse effects (eg, hot flushes, sweats, sleep disturbance). Similarly, functional ovarian suppression with gonadotropin-releasing factor analogues in pre- or peri-menopausal women with hormone receptor-positive tumors confers benefits comparable with chemotherapy. National Comprehensive Cancer Network (NCCN) guidelines indicate ovarian ablation or suppression are both options in combination with endocrine therapy for premenopausal women who have invasive or recurrent disease and are recommended for premenopausal women with systemic disease.10

For post-menopausal women with osteoporosis or at high-risk for invasive breast cancer, raloxifene is an alternative treatment for invasive cancer risk reduction. Efficacy equals that of tamoxifen, and risk of endometrial hyperplasia is markedly reduced. Currently, raloxifene is not indicated for treatment of invasive breast cancer, reduction of breast cancer recurrence risk, or noninvasive breast cancer risk reduction.11

The pharmacogenomics of tamoxifen have been most often studied in postmenopausal women who have estrogen receptor-positive tumors and require endocrine therapy to prevent recurrence. For this population, the NCCN 2017 guidelines for the management of breast cancer includes a number of statements related to the use of adjuvant tamoxifen (among other endocrine therapies), which are summarized in Table 1.10:

---

### Table 1. 2017 NCCN Guidelines for Adjuvant Endocrine Therapy for Postmenopausal Women with Breast Cancer

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal at Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen for 5 years (with or without ovarian suppression), followed by AI for 5 years if</td>
<td>1</td>
</tr>
</tbody>
</table>
**Recommendation**

<table>
<thead>
<tr>
<th>Postmenopausal</th>
<th>COR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen for 5 years(^a) (with or without ovarian suppression)(^b) followed by consideration for tamoxifen for 5 years(^b) if postmenopausal</td>
<td>2A</td>
</tr>
<tr>
<td>Tamoxifen for 5 years(^a) (with or without ovarian suppression)(^b) followed by consideration for tamoxifen for 5 y OR no further therapy if still premenopausal</td>
<td>2A</td>
</tr>
</tbody>
</table>

**Postmenopausal at diagnosis**

| Tamoxifen for 2-3 years followed by tamoxifen for a total of 5 years of endocrine therapy | 1 |
| Tamoxifen for 2-3 years followed by AI for a total of 5 years of endocrine therapy | 1 |
| Tamoxifen for 2-3 years followed by up to 5 years of an AI\(^c\) | 2A overall |
| Tamoxifen for 2-3 years followed by 1 of 3 AIs to complete 5 years of endocrine therapy | 2B |
| Tamoxifen for 4.5-6 years followed by AI for 5 years | 1 |
| Tamoxifen for 4.5-6 years followed by consideration for tamoxifen for 5 more years | 2A |
| In women with a contraindication to AIs, or who decline or are intolerant of AIs, consideration for tamoxifen for 5 years of tamoxifen for up to 10 years | 1 |

AI: aromatase inhibitor; COR: category of recommendation.

\(^a\) COR 1.

\(^b\) COR 2A.

\(^c\) COR 2B.

---

**Pharmacologic Inhibitors of Metabolic Enzymes**

CYP2D6 activity may be affected not only by genotype but also by co-administered drugs that block CYP2D6 function. Studies of selective serotonin reuptake inhibitors (SSRIs) in particular have shown that fluoxetine and paroxetine, but not sertraline, fluvoxamine, or venlafaxine, are potent CYP2D6 inhibitors.\(^{12-14}\) Some individuals treated with fluoxetine or paroxetine changed from EM phenotype to PM.\(^{12}\) The degree of inhibition may depend on SSRI dose.

Thus, CYP2D6 inhibitor use must be considered in assigning CYP2D6 functional status, and potent CYP2D6 inhibitors may need to be avoided when tamoxifen is administered.

---

**Summary of Evidence**

For individuals who are treated with tamoxifen for breast cancer or have a high risk of breast cancer and receive testing for CYP2D6 metabolizer status by CYP2D6 genotyping, the evidence
includes multiple retrospective studies, post hoc analysis of randomized controlled trials, and meta-analysis. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, medication use, and treatment-related morbidity. Published data on the association between CYP2D6 genotype and tamoxifen treatment outcome have yielded inconsistent results. Some inconsistencies in the literature may be due to differences across studies in the types of additional therapies patients received, how many and which CYP2D6 alleles were tested, tissue type examined (tumor or germline DNA), and coadministered CYP2D6 inhibitors. The largest, most well-designed studies do not support a significant association between CYP2D6 genotype and tamoxifen treatment outcomes. At present, the clinical utility of CYP2D6 testing is also poorly defined. An interventional study of CYP2D6-specific tamoxifen dosing found that personalized dosing was associated with changes in endoxifen level, but it has not been clearly demonstrated that endoxifen level is associated with improved outcomes. It is not known whether clinical management guided by CYP2D6 genotyping improves patient outcomes such as appropriate selection of a treatment strategy that would reduce the rate of recurrence, improve disease-free survival or overall survival, or reduce adverse events. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some trials that might impact this policy are listed in Table 2.

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01220076</td>
<td>Phase II Study Evaluating According to the Polymorphism of CYP2D6, the Rate of Biological Response to Treatment With Tamoxifen (TAM) Administered in Pre-operative Situation in Patients With Breast Cancer Non Metastatic HR+</td>
<td>265</td>
<td>Nov 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT01357772</td>
<td>Randomized Placebo-controlled Phase III Trial of Low dose Tamoxifen in Women With Breast Intraepithelial Neoplasia</td>
<td>1400</td>
<td>Dec 2023</td>
</tr>
</tbody>
</table>

NCT: National Clinical Trial
Practice Guidelines and Position Statements

**National Comprehensive Cancer Network**

Regarding the use of CYP2D6 genetic testing before prescribing tamoxifen, the National Comprehensive Cancer Network breast cancer guidelines (v.2.2017) state: “CYP2D6 genotype testing is not recommended in women who are considering tamoxifen.”

**The American Society of Clinical Oncology**

A 2010 guideline update from the American Society of Clinical Oncology (ASCO) “recommend[ed] against using CYP2D6 genotype to select adjuvant endocrine therapy.... [and] encouraged caution with concurrent use of CYP2D6 inhibitors....” A 2013 guideline update from ASCO affirmed that position: “Data from the NSABP-P1 and STAR trials do not support the use of CYP2D6 testing to identify women not likely to benefit from tamoxifen therapy for breast cancer prevention.”

**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**

The AmpliChip CYP450 Test (Model 04381866190, Roche) was cleared for marketing by the FDA through the 510(k) process (K042259) and can be used to identify CYP2D6 genotype.

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). CYP2D6 genotyping assays are also 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


42. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). CYP2D6 Pharmacogenomics of Tamoxifen Treatment. TEC Assessments 2013;Volume 28:Tab 8. PMID


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/13/11</td>
<td>Add to Pathology/Laboratory Section - New medical policy with investigational policy statement. No specific code. Policy approved with 90-day hold for provider notification.</td>
</tr>
<tr>
<td>11/17/11</td>
<td>Reviewed and recommended by OAP on November 17, 2011.</td>
</tr>
<tr>
<td>01/24/12</td>
<td>Codes 81225 – 81227 added.</td>
</tr>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.51 (previously 2.04.51) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>06/26/12</td>
<td>Replace policy. Policy updated with literature search. References 25-32, 38, 39, 48-50 added. No change to policy statement.</td>
</tr>
<tr>
<td>10/10/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>01/10/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT code 81200 – 81479 and 81599, effective 1/1/13, added to the policy.</td>
</tr>
<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>08/16/13</td>
<td>Replace policy. Policy updated with literature search through May 13, 2013. Reference 51 added. Reference 10 updated. No change to policy statement.</td>
</tr>
<tr>
<td>07/31/14</td>
<td>Annual Review. Policy updated with literature review through March 2014. References 9, 12, 18-19, 34-38, 46, 63-73, 75 added; references 10-11 updated; others renumbered/removed. Policy statement unchanged.</td>
</tr>
<tr>
<td>12/01/14</td>
<td>Update Related Policies. Add 12.04.38.</td>
</tr>
<tr>
<td>07/14/15</td>
<td>Annual Review. Policy updated with literature review through April 21, 2015. References 37, 39, 43-44, 69, 74 added. Policy statements unchanged. ICD-10-CM codes removed; informational only.</td>
</tr>
<tr>
<td>04/01/16</td>
<td>Update Related Policies. Remove 12.04.38 as it was deleted and replaced with 12.04.517.</td>
</tr>
<tr>
<td>10/01/16</td>
<td>Annual Review, approved September 13, 2016. Policy updated with literature review through June 13, 2016; reference added; policy statement unchanged.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>08/01/17</td>
<td>Annual Review, approved July 25, 2017. Policy moved to new format. Policy updated with literature review through April 25, 2017; reference 64 added. Policy revised with updated genetics nomenclature; policy statement otherwise unchanged.</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.

**Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  • Qualified sign language interpreters
  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

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)
Complaint forms are available at

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.
Call 800-722-1471 (TTY: 800-842-5357).

علمى (Amharic):
لا يُمنع الملكي من التعامل مع الإخوان على أساس العرق، اللون، الجنسية، العمر، الإعاقة، أو الجنس.

العربية (Arabic):
يحظر هذا الإذاعة معلومات هامة. قد يحتوي هذا الإذاعة معلومات مهمة بخصوص طبيك أو
العلاقية التي تريد الحصول عليها من خلال الاتصال بمكتب Premera Blue Cross.
لا توجد هناك ترجمة معينة لترجمة الإذاعة.

프리머라 블루크로스 (Korean):
Premera Blue Cross는 소유한 블루크로스 및 매피크로스를 포함한 친구와 자매의
개인 정보를 보호합니다. 사기 좋은 정보가 없는 경우, 원하시는 언어로 제공하는
어린이의 정보를 제공합니다.

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的
申請或辦案的重要訊息。本通知可能有重要日期。您可能需要在截止日期
之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的
母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):
Beekisini kun odeefannoo barbarchaasaa qaba. Beekisiti kun sagantaa
yooan karaa Premera Blue Cross tiin tajajila keessaa italaashiile
odeefannoo barbarchaasihaa qabaachuu danda'a. Guyyaaawaa murteessaa
ta' an beekisita kana keessatti ilaala. Tairi kaffaltiidaan deeggarammu
yooan tajajila fayyaa keessanif guyyaa dhumaa irratti wanti raawwatan
jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afana keessanin
odeefannoo argachuu fi deeggarsa argachuu miga ni qabaaatu.
Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) ti bilbilaa.

Français (French):
Cet avis a des importantes informations. Cet avis peut avoir des informations
sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross.
Le présent avis peut contenir des dates clés. Vous
devrez peut-être prendre des mesures par certains délais pour maintenir
votre couverture de santé ou d'aide avec les coûts. Vous avez le droit
d'obtenir cette information et de l'aide dans votre langue à aucun coût.
Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyol ayisyen (Creole):
Avi sila a gen enfômasyon Enpòtan liadan. Avi sila a kapab genyen
 enfômasyon enpòtan konsènan aplikasyon w l'an osawa konèsan kouvèti
 asirans lan atravé Premera Blue Cross. Kapab genyen dat ki en epòtan nan
 avi sila a. Ou ka gen pou pran kék aksyon avan seten dat limit pou ka
genitye kouvèti asirans sante w l'osawa pou yo ka ede w avelk depans yo. Se
dwa w pou reseven enfômasyon 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):
Diese Benachrichtigung enthält wichtige Informationen. Diese
Benachrichtigung enthält unter Umständen wichtige Informationen
bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross.
Suchen Sie nach eventuellen wichtigen Terminen in dieser
Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln
müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten
zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen
in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471
(TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tsjhay xo no muaj cov ntsiab lus tseem ceeb. Tej zaum
tsab ntawv tsjhay xo no muaj cov ntsiab lus tseem ceeb bxog kog daim ntawv
thov kev pas loeg yoy kov kev pas cuam loeg ntsawm Premera Blue Cross.
Tej zaum muaj cov hnnv tseem ceeb cuam sas rau hauv daim ntawv no.
Tej zaum kog koy juaw tau uu qee yam pas kog koy tuas bpuh
dhau cov cajj nyoyng uas teev tseng rau hauv daim ntawv no mas kog koy
juaw tuas baas kev pas cuam khou kho mob yov ngob kev pas yam mes tej
qji kho mob ntawv. Kog muaj cai kom lawv muab cov ntsiab lus no uas tuaw msab
uu kog hom lus pub dawb rau kog. Hu rau 800-722-1471
(TTY: 800-842-5357).

Ilkoo (Ilocano):
Daytoy a Pakdaaar ket naglaon iti Napateg nga Impormasion. Daytoy a
pakdaaar malabian nga adda ket naglaon iti napateg nga impormasion
maipanggep iti aplikasyonovo woy coverage babaen iti Premera Blue Cross.
Daytoy ket malabian dagiti importante a pelsa iti daytoy a pakdaaar.
Malabian nga adda rumbeng nga aramidendo nga adda sakkay dagiti
partikular a naituding nga aldaw tapno mapatagalinneyo ti coverage ti
salay-ano woy woy tulong kadagit gastos. Adda karbenganyo a mangala iti
daytoy nga impormasion ken tulong iti bukodyo a pagasaa nga awan ti
bayadanyo. 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.
Chiamala 800-722-1471 (TTY: 800-842-5357).

037338 (07-2016)