Introduction

Fluorouracil (5FU) is a chemotherapy used to treat different cancers. These are colon, rectum, breast, stomach, and pancreatic cancer. As with all chemotherapies, the goal is to give enough medication to treat the cancer without causing ongoing harm to the rest of the body. Blood tests have been developed that try to give information about how much 5FU to use during each treatment. These tests are investigational. This means they are not proven. There is not enough published medical evidence to show that these blood tests lead to better results. Similarly, genetic tests have been created that try to show how the body processes (metabolizes) 5FU. These genetic tests are investigational. There is not enough medical evidence to show if these tests provide enough useful information to affect overall health.

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.
## Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>My5-FU™</td>
<td>My5-FU™ assay testing or other types of assays for determining 5-fluorouracil (5-FU) area under the curve in order to adjust 5-FU dose for colorectal cancer patients or other cancer patients is considered investigational.</td>
</tr>
<tr>
<td></td>
<td><strong>Note:</strong> My5-FU™ was previously known as OnDose® (Myriad Genetics under license from Saladax Biomedical); and the TheraGuide® test is no longer commercially available.</td>
</tr>
<tr>
<td>DPYD or TYMS genes</td>
<td>Testing for genetic variants in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) genes to guide 5-FU dosing and/or treatment choice in patients with cancer is considered investigational.</td>
</tr>
</tbody>
</table>

## Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
</tbody>
</table>
| 81400 | Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) that includes the following test:  
  • DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), IVS14+1G>A variant |
| 81401 | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) ) that includes the following test:  
  • TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), tandem repeat variant |
| 84999 | Unlisted chemistry procedure                                                |
| **HCPCS** |                                                                                  |
| S3722 | Dose optimization by area-under-the-curve (AUC) analysis for infusional 5-fluorouracil (5-FU) that is specific for the My5-FU test. |

**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

**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.

**Evidence Review**

**Description**

Variability in systemic exposure to 5-fluorouracil (5-FU) is thought to directly impact 5-FU tolerability and efficacy. The standard approach is dosing according to body surface area. Two alternative approaches have been proposed for modifying use of 5-FU: (1) dosing based on determined area under the curve serum concentration target and (2) genetic testing for variants affecting 5-FU metabolism. For genetic testing, currently available polymerase chain reaction tests assess specific variants in genes encoding dihydropyrimidine reductase (DPYD) and thymidylate synthase (TYMS) in the catabolic and anabolic pathways of 5-FU metabolism, respectively.

**Background**

**5-fluorouracil**

The agent 5-fluorouracil (5-FU) is a widely used antineoplastic chemotherapy drug that targets thymidylate synthase (TYMS) enzyme, which is involved in DNA production. 5-FU has been used
for many years to treat solid tumors (eg, colon and rectal cancer, head and neck cancer). In general, the incidence of grade 3 or 4 toxicity (mainly neutropenia, diarrhea, mucositis, and hand-foot syndrome) increases with higher systemic exposure to 5-FU. Several studies also have reported statistically significant positive associations between 5-FU exposure and tumor response. In current practice, however, 5-FU dose is reduced when symptoms of severe toxicity appear, but is seldom increased to promote efficacy.

Based on known 5-FU pharmacology, it is possible to determine a sampling scheme for area under the curve (AUC) determination and to optimize an AUC target and dose-adjustment algorithm for a particular 5-FU chemotherapy regimen and patient population. For each AUC value or range, the algorithm defines the dose adjustment during the next chemotherapy cycle most likely to achieve the target AUC without overshooting and causing severe toxicity.

In clinical research studies, 5-FU blood plasma levels most recently have been determined by high-performance liquid chromatography or liquid chromatography coupled with tandem mass spectrometry. Both methods require expertise to develop an in-house assay and may be less amenable to routine clinical laboratory settings.

**Measuring Exposure to 5-FU**

**Laboratory Testing**

Patient exposure to 5-FU is most accurately described by estimating the AUC, the total drug exposure over a defined period of time. 5-FU exposure is influenced by method of administration, circadian variation, liver function, and the presence of inherited dihydropyrimidine reductase (DPYD)-inactivating genetic variants that can greatly reduce or abolish 5-FU catabolism. As a result, both inter- and intrapatient variability in 5-FU plasma concentration during administration is high.

Determination of 5-FU AUC requires complex technology and expertise that may not be readily available in a clinical laboratory setting. In the United States, a commercial immunoassay (My5-FU) can quantify plasma 5-FU concentration from a blood sample drawn during continuous infusion at steady state (18-44 hours after the start of infusion) and provides a dose-adjustment algorithm to maintain plasma 5-FU AUC between 20 and 30 mg/h/L during the next cycle.¹
**Genetic Testing**

5-FU is a pyrimidine antagonist, similar in structure to the normal pyrimidine building blocks of RNA (uracil) and DNA (thymine). More than 80% of administered 5-FU is inactivated and eliminated via the catabolic pathway; the remainder is metabolized via the anabolic pathway.

Catabolism of 5-FU is controlled by the activity of DPYD. Because DPYD is a saturable enzyme, the pharmacokinetics of 5-FU are strongly influenced by the dose and schedule of administration. For example, 5-FU clearance is faster with continuous infusion than with bolus administration, resulting in very different systemic exposure to 5-FU during the course of therapy. Genetic variants in DPYD, located on chromosome 1, can lead to reduced 5-FU catabolism and increased toxicity. Many variants have been identified (eg, IVS14+1G>A [also known as DPYD*2A], 2846A>T [D949V]). DPYD deficiency is an autosomal codominantly inherited trait.

The anabolic pathway metabolizes 5-FU to an active form that inhibits DNA and RNA synthesis by competitive inhibition of TYMS or by incorporation of cytotoxic metabolites into nascent DNA. Genetic variants in TYMS can cause tandem repeats in the TYMS enhancer region (TSER). One variant leads to 3 tandem repeats (TSER*3) and has been associated with 5-FU resistance due to increased tumor TYMS expression compared with the TSER*2 variant (2 tandem repeats) and wild-type forms.

**Summary of Evidence**

For individuals who have cancer for whom treatment with 5-FU is indicated who receive laboratory assays to determine 5-FU area under the curve, the evidence includes randomized controlled trials (RCTs), observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity and treatment-related morbidity. Several analyses of patients with colorectal cancer have evaluated clinical validity. One study, for example, found that the rate of severe toxicity was significantly lower in patients with stage II and III cancer who chose pharmacokinetic monitoring vs BSA monitoring, but progression-free survival did not differ between groups in patients with stage IV or recurrent cancer. No RCTs or nonrandomized comparative studies were identified comparing health outcomes in cancer patients who did and did not have 5-FU dose adjustment using the My5-FU assay and who were treated with chemotherapy regimens used in current clinical practice. A systematic review of the available literature found a significantly higher response rate with BSA-based monitoring and no significant difference in toxicity. Most data derived from observational studies and the randomized controlled trials were conducted in the 1980s when different
chemotherapy protocols were used. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer for whom treatment with 5-FU is indicated who receive genetic testing for variants (eg, in \textit{DPYD} and \textit{TYMS}) affecting 5-FU metabolism, the evidence includes observational studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. A TEC Assessment (2010) concluded that \textit{DPYD} and \textit{TYMS} variant testing had poor prognostic capacity to identify patients likely to experience severe 5-FU toxicity. Since publication of that Assessment, no prospective trials comparing efficacy and toxicity outcomes in patients who did and did not undergo pretreatment \textit{DPYD} and/or \textit{TYMS} testing have been published. One study compared outcomes in patients undergoing pretreatment \textit{DPYD} testing with historical controls who did not receive testing. In that study, rates of grade 3 or higher toxicity were lower in patients who had genetic testing; however, the study was not randomized and lacked concurrent controls. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review 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>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AUC-guided dosing of 5-FU</strong></td>
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<tr>
<td>NCT00943137</td>
<td>The Optimisation of 5-Fluorouracil Dose by Pharmacokinetic Monitoring in Asian Patients With Advanced Stage Cancer</td>
<td>55</td>
<td>Jun 2017 (unknown)</td>
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<tr>
<td>NCT02055560</td>
<td>Retrospective Data Comparison of Toxicity and Efficacy in Colorectal Cancer (CRC) Patients Managed With and Without 5-FU Exposure Optimization Testing</td>
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<td>Dec 2017 (unknown)</td>
</tr>
<tr>
<td><strong>DPYD and/or TYMS testing before use of fluoropyrimidines</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NCT02324452</td>
<td>Safety, Feasibility and Cost-effectiveness of Genotype-directed Individualized Dosing of Fluoropyrimidines</td>
<td>1250</td>
<td>Mar 2018 (ongoing)</td>
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<tr>
<td>NCT00131599</td>
<td>Thymidylate Synthase Polymorphisms as a Predictor of</td>
<td>104</td>
<td>July 2017</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT02138617</td>
<td>Genotype-Directed Phase II Study Of Higher Dose Of Irinotecan In First-Line Metastatic Colorectal Cancer Patients Treated With Folfiri Plus Bevacizumab</td>
<td>100</td>
<td>May 2022</td>
</tr>
</tbody>
</table>

AUC: area under the curve; 5-FU: 5-Fluorouracil; NCT: national clinical trial.

*a Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

**National Comprehensive Cancer Network**

Although current National Comprehensive Cancer Network guidelines acknowledge that the “selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex,” the Network does not recommend use of area under the curve guidance for 5-fluorouracil (5-FU) dosing or genetic testing for DPYD and/or TYMS variants in patients with colon, rectal, breast, gastric, pancreatic cancer, or head and neck cancers.

**Clinical Pharmacogenetics Implementation Consortium**

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed in 2009 as a shared project between PharmGKB, an internet research tool developed by Stanford University, and the Pharmacogenomics Research Network of the National Institutes of Health. CPIC (2013) published an evidence-based guideline for DPYD genotype and fluoropyrimidine dosing. The guideline did not address testing.

A 2017 update to the CPIC guidelines was published by Amstutz et al (2018). As in 2013, the primary focus of the guidelines was on the DPYD genotype and implications for dosing of fluoropyrimidine. In the 2017 update, CPIC noted that genetic testing for DPYD may include “resequencing of the complete coding regions” or may be confined to analysis of particular risk variants, among which CPIC listed the c.190511G>A, c.1679T>G, c.2846A>T, and c.1129-5923C>G variants, as affecting 5-FU toxicity. The guideline further noted that, while other genes (TYMS, MTHFR) may be tested for variants, the clinical utility of such tests is yet unproven. In patients who have undergone genetic testing and who are known carriers of a DPYD risk variant, the guidelines recommended that caregivers strongly reduce the dosage of 5-FU-based
treatments, or exclude them, depending on the patient's level of DPYD activity. CPIC advised follow-up therapeutic drug monitoring to guard against underdosing and cautioned that genetic tests could be limited to known risk variants and, therefore, not identify other DPYD variants.

**National Institute for Health and Care Excellence**

The National Institute of Health and Care Excellence (2014) published evidence-based diagnostics guidance on the 5-FU assay for 5-FU chemotherapy dose adjustment. The guidance stated: “The My5-FU assay is only recommended for use in research for guiding dose adjustment in people having fluorouracil chemotherapy by continuous infusion. The My5-FU assay shows promise and the development of robust evidence is recommended to demonstrate its utility in clinical practice.”

**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. My5-FU™ (Saladax Biomedical) and genetic testing for variants in DPYD and TYMS for predicting the risk of 5-FU toxicity and chemotherapeutic response (ARUP Laboratories) are 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**


26. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Pharmacogenetic Testing to Predict Serious Toxicity From 5-Fluorouracil (5-FU) for Patients Administered 5-FU-Based Chemotherapy for Cancer. TEC Assessments. 2010;24:Tab 13.


<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, considered investigational. No specific code. Reviewed by OAP on May 12, 2011. Policy approved with 90-day hold for provider notification.</td>
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<td>01/25/12</td>
<td>HCPCS code S3722 added.</td>
</tr>
<tr>
<td>05/22/12</td>
<td>Replace policy. Policy updated with literature search. References 20-22 added. No change to policy statement.</td>
</tr>
<tr>
<td>09/18/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>05/28/13</td>
<td>Replace policy. Rationale section updated based on a literature review through February 2013. References 18 and 21 added; others renumbered or removed. Policy statement unchanged.</td>
</tr>
<tr>
<td>05/12/14</td>
<td>Annual Review. Title changed to include genetic testing. First investigational policy statement test name OnDose® changed to new test name My5-FU™. New investigational policy statement for TheraGuide® testing for genetic mutations in DPYD or TYMS added. Policy updated with literature review through February 17, 2014. References 2, 4-7, 12, 15-16, 30-44 added; references 8, 17, 29 updated. Policy statements changed as noted. ICD-10 codes removed to support ICD-10 mapping project.</td>
</tr>
<tr>
<td>06/01/16</td>
<td>Annual Review, approved May 10, 2016. Policy updated with literature review through February 2, 2016; references 27, 29, and 45 added. “TheraGuide” removed from policy statement since this test is no longer commercially available. Policy statements 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). ©2018 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.
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  • Qualified interpreters
  • Information written in other languages

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Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email ComplaintsDepartmentinquines@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).

Oromoo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Azi sila a gen Enfòmasyon Enpòtan ladan. Azi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan osawa konsèn kouviiti asirans lan atravay Premera Blue Cross. Kapab genyen dat ki enpòtan nan azi sila a. Ou ka gen pou pran kék aksyon avan seten dat limit pou ka kentbe kouviiti asirans sante w la osawa pou yo ka ede w avak depans yo. Se dwa w pou resewwa enfòmasyon sa a ak asisants nan lang ou pale a, sa ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

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Hmoob (Hmong):

Ilokano (Ilocano):
Dayttoy a Pakdaaket kat naglaon iti Napateg nga Impomorsion. Dayttoy a pakdaaket mabalin nga adda kat naglaon iti napateg nga impomorsion maipanggep ngi aplikasyonyo nyoong coverage baben a Iti Premera Blue Cross. Dayttoy ket mabalin dagiti importante a pelsa iti dayttoy a pakdaaket. Mabalin nga adda rumbeng nga aramidenyo nga adda sabbay dagiti partikular a nalitdung nga adda aldaw tapno mapagtalainedyo ti coverage ti salan-ayyo nyoong tulong kadagit gastos. Adda karbenganyo a mangala iti dayttoy nga impomorsion ken tulong ti bukdoyo a pagasasao nga awan ti bayadanoy. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. 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).
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Russian (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, возможно, потребуется принять меры к определенному предельному срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

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Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cubrimiento a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar 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).

Portuguese (Portuguese):

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):


Filipino (Tagalog):

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagkakatulong na paglabas o kaso nga maalala ang Premera Blue Cross. Maaring magaangalang ka na magsagawa ng kabang sa ilang mga tawo ang panahon unang maparalan ang iyong aplikasyon o pagkakatulong na tulong sa iyong kaso o kaso nga maalala ang Premera Blue Cross.

Tiếng Việt (Vietnamese):

Thông báo này cũng có thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia học bổng hoặc bảo hiểm của quý vị qua chuẩn trình Premera Blue Cross. Xin xem ngay quan trọng thông báo này. Quý vị có thể phải thực hiện thông báo đúng trong thời hạn để đủ điều bảo hiểm sẽ có hiệu lực hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).