MEDICAL POLICY – 2.04.125
Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer

BCBSA Ref. Policy: 2.04.125
Effective Date: May 1, 2017
Last Revised: Oct. 24, 2017
Replaces: N/A

RELATED MEDICAL POLICIES:
2.04.62 Multimarker Serum Testing Related to Ovarian Cancer

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

Genes in our DNA tell a cell how to make proteins. The study of proteins in a cell is called “proteomics”. Doing tests on the proteins in a cell (“proteomic testing”) may help to identify which drugs might be helpful in treating non-small cell lung cancer and how aggressive the cancer is. Proteomic testing used for this and all other reasons is unproven (investigational). Medical studies have not determined the types of patients in which proteomic testing could predict the course of the disease. Studies also have not shown that patients whose treatments were chosen based on proteomic testing survived longer than those whose treatments were selected without proteomic testing.

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.
Proteomic testing is considered investigational for all uses in the management of non-small cell lung cancer.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival</td>
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<tr>
<td>81538</td>
<td>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).</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
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</table>

**Note:**

Proteomic testing has been proposed as a way to predict survival outcomes and the response to and selection of targeted therapy for patients with non-small cell lung cancer (NSCLC). One commercially available test, the VeriStrat® assay, has been investigated as a predictive marker for response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).
Background

Non-small Cell Lung Cancer

Lung cancer is the leading cause of cancer death in the United States, with an estimated 221,200 new cases and 158,040 deaths due to the disease in 2015.\(^1\) Non-small cell lung cancer (NSCLC), which includes nonsquamous carcinoma (adenocarcinoma, large cell carcinoma, other cell types) and squamous cell carcinoma, causes about 85% of lung cancer cases. Treatment approaches generally include surgery, radiotherapy, and chemotherapy, either alone or in combination, depending on the disease stage and tumor characteristics. However, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication, and up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have brief responses, with a median time to progression of 3 to 5 months.\(^2\) Second-line chemotherapy after platinum-based chemotherapy is associated with small improvements in time to progression. Genetic abnormalities in NSCLC and the development of therapies targeted to those abnormalities have prompted interest in tests to predict response to targeted therapies.

Genetic Alterations in NSCLC

Several common genetic alterations in NSCLC have been targets for drug therapy, the most well-established of which is the use of tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR), and crizotinib targeting the ALK gene rearrangement.

EGFR Variants in NSCLC

The EGFR, a receptor tyrosine kinase (TK), is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR signaling either prevent ligand binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small molecule TKIs). These targeted therapies dampen signal transduction through pathways downstream to the EGFR, such as the RAS/RAF/MAPK cascade. RAS proteins are G-proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Variants in 2 regions of the EGFR gene, including small deletions in exon 19 and a point mutation in exon 21 (L858R), appear to predict tumor response to TKIs such as erlotinib.
prevalence of EGFR variants in NSCLC varies by population, with the highest prevalence in nonsmoking, Asian women, with adenocarcinoma, in whom EGFR variants have been reported to be up to 30% to 50%. The reported prevalence of EGFR mutations in lung adenocarcinoma patients in the United States is approximately 15%.

**ALK Variants**

In about 2% to 7% of NSCLC patients in the United States, tumors express a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 gene and the anaplastic lymphoma kinase gene (EML4-ALK), which is created by an inversion on chromosome 2p. The EML4 fusion leads to ligand-independent activation of ALK, which encodes a receptor TK whose precise cellular function is not completely understood. EML4-ALK mutations are more common in never-smokers or light smokers, tend to be associated with younger age of NSCLC onset, and typically do not occur in conjunction with EGFR variants.

Testing for the EML4-ALK fusion gene in patients with adenocarcinoma-type NSCLC is used to predict response to the small molecule TKI crizotinib.

**Other Genetic Mutations in NSCLC**

Other genetic variants have been identified in subsets of patients with NSCLC, which are summarized in Table 1. The role of testing for these mutations to help select targeted therapies for NSCLC is less well-established than for EGFR variants.

### Table 1: Non-EGFR Mutations in NSCLC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Function</th>
<th>Estimated Mutation Prevalence in NSCLC</th>
<th>Patient and Tumor Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>Encodes RAS proteins; variants associated with constitutively activated protein</td>
<td>20%-30%</td>
<td>Adenocarcinomas Heavy smokers</td>
</tr>
<tr>
<td>ROS1</td>
<td>Encodes a receptor TK in the insulin receptor family</td>
<td>0.9%-3.7%</td>
<td>Adenocarcinoma Never smokers</td>
</tr>
<tr>
<td>RET</td>
<td>Proto-oncogene that encodes a receptor TK</td>
<td>0.6%-2%</td>
<td></td>
</tr>
</tbody>
</table>

Page | 4 of 15
<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Function</th>
<th>Estimated Mutation Prevalence in NSCLC</th>
<th>Patient and Tumor Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>Oncogene that encodes a receptor TK that is activated in response to binding of hepatocyte growth factor</td>
<td>2-4% of previously untreated NSCLC; 5%-20% of patients with acquired resistance to EGFR TKIs</td>
<td>Patients with acquired resistance to EGFR TKIs</td>
</tr>
<tr>
<td>BRAF</td>
<td>Serine-threonine kinase downstream from RAS in RAS-RAF-ERK-MAPK pathway</td>
<td>1%-3% of adenocarcinomas</td>
<td>Heavy smokers</td>
</tr>
<tr>
<td>HER</td>
<td>HER (EGFR) family of TK receptors; dimerizes with EGFR family members when activated</td>
<td>1%-2% of NSCLC</td>
<td>Adenocarcinomas Nonsmoking women</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Intracellular signaling pathway</td>
<td>≈4% of NSCLC</td>
<td></td>
</tr>
</tbody>
</table>

EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; TK: tyrosine kinase; TKI: tyrosine kinase inhibitor.

**Targeted Treatment Options**

**EGFR-Selective Small Molecule TKIs**

Three orally administered EGFR-selective small molecule TKIs have been identified for use in treating NSCLC: gefitinib (Iressa®, AstraZeneca), erlotinib (Tarceva®, OSI Pharmaceuticals), and afatinib (Gilotrif™, Boehringer Ingelheim). Although the Food and Drug Administration (FDA) originally approved gefitinib, in 2004, a Phase III trial suggested gefitinib was not associated with a survival benefit. In May 2005, the FDA revised gefitinib labeling, further limiting its use to patients who had previously benefitted or were currently benefiting from the drug; no new patients were to be given gefitinib. However, in July 2015, the FDA approved gefitinib as first-line treatment for patients with metastatic NSCLC for patients with EGFR-mutated tumors. Erlotinib and afatinib also have approval by the FDA.

In 2016, osimertinib (Tagrisso, AstraZeneca), an irreversible selective EGFR inhibitor that targets T790M mutation-positive NSCLC, received FDA approval for patients with T890M-mutation-positive NSCLC who have progressed on an EGFR TKI.

A 2013 meta-analysis of 23 trials of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC reported improved progression-free survival (PFS) in EGFR mutation-positive patients treated with EGFR TKIs in the first- and second-line settings and as maintenance therapy.\(^5\) Comparisons were chemotherapy, chemotherapy and placebo, and placebo in the first-line,
second-line, and maintenance therapy settings. Among EGFR mutation–negative patients, PFS was improved with EGFR TKIs compared with placebo for maintenance therapy but not in the first- and second-line settings. Overall survival (OS) did not differ between treatment groups in either mutation-positive or mutation-negative patients. Statistical heterogeneity was not reported for any outcome. The authors concluded that EGFR mutation testing is indicated to guide treatment selection in NSCLC patients.

On the basis of the results of 5 Phase III randomized controlled trials, the American Society of Clinical Oncology recommended that patients with NSCLC who are being considered for first-line therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumor tested for EGFR mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.3

The primary role for TKIs in NSCLC is for EGFR mutation–positive patients with advanced NSCLC. The use of TKIs in NSCLC in EGFR mutation–negative patients is controversial. The TITAN trial demonstrated no significant differences in OS between erlotinib and chemotherapy as second-line treatment for patients unselected on the basis of EGFR mutation status, with fewer serious adverse events in erlotinib-treated patients.6 Karampeazis et al. reported similar efficacy between erlotinib and standard chemotherapy (pemetrexed) for second-line therapy in patients unselected on the basis of EGFR mutation status.7 In contrast, in the TAILOR trial, standard chemotherapy was associated with longer OS than erlotinib for second-line therapy in patients with wild-type EGFR.8 Auliac et al. compared sequential erlotinib plus docetaxel with docetaxel alone as second-line therapy among patients with advanced NSCLC and EGFR wild-type or unknown status.9 Based on a Simon’s optimal 2-stage design, the erlotinib plus docetaxel strategy was rejected, with 18 of 73 patients in the erlotinib plus docetaxel arm achieving PFS at 15 weeks compared with 17 of 74 patients in the docetaxel arm.

In 2016, Cicenas et al reported results of the IUNO RCT, which compared maintenance therapy with erlotinib followed by second line chemotherapy if progression occurred to placebo followed by erlotinib if progression occurred in 643 patients with advanced NSCLC with no known EGFR variant.10 Because there were no significant differences between groups in terms of PFS, objective response rate, or disease control rate, maintenance therapy with erlotinib in patients without EGFR variants was not considered efficacious.

**Anti-EGFR Monoclonal Antibodies**

For the treatment of KRAS-mutated NSCLC, anti-EGFR monoclonal antibodies have been investigated as possible treatment options. Available anti-EGFR monoclonal antibodies include
cetuximab and panitumumab. The benefits of cetuximab in NSCLC have been questioned by the National Comprehensive Cancer Network.\textsuperscript{1} Panitumumab is not generally used in NSCLC.

**Programmed Death Ligand 1 Inhibitors**

Some tumors, including some NSCLCs, express a programmed death ligand 1 (PD-L1) on the cell surfaces to interact with host T-cells and evade the immune system. Several humanized monoclonal antibodies have been developed to act as immune checkpoint inhibitors by interfering with this interaction, to interact with the PD-L1, block the cancer/T-cell interaction, and thus act as immune checkpoint inhibitors. Pembrolizumab and nivolumab, which inhibit the programmed death 1 receptor, and atezolizumab, which inhibits the PD-L1, are used in NSCLC that have PD-L1 expression on its cells.

**Other Targeted Therapies**

Crizotinib is a novel MET, ROS1, and ALK TKI, and associated with improved progression-free survival in patients with advanced NSCLC who are ALK gene rearrangement–positive.\textsuperscript{11} Crizotinib is considered first-line therapy for advanced ALK-positive lung adenocarcinoma.\textsuperscript{1} Two other small molecule TKIs, designed to selectively bind to and inhibit ALK activation, have FDA approval: ceritinib and alectinib.

Proposed targeted therapies for other genetic alterations in NSCLC are trastuzumab for HER2 variants, crizotinib for MET amplification and ROS-1 rearrangement, vemurafenib and dabrafenib for BRAF variants, and cabozantinib for RET rearrangements.

**Proteomics Testing in Selecting Targeted Treatment for NSCLC**

The term proteome refers to the entire complement of proteins produced by an organism or cellular system, which may vary over time and in response to selected stressors, and proteomics refers to the large-scale comprehensive study of a specific proteome.\textsuperscript{12} A cancer cell’s proteome is related to its genome and to genomic alterations, but may not be static over time. The proteome may be measured with mass spectrometry or protein microarray. For cancer, proteomic signatures in the tumor or in bodily fluids (ie, pleural fluid or blood) other than the tumor have been investigated as a biomarker for cancer activity.
For NSCLC, 1 commercially available serum-based test, VeriStrat® (Biodesix, Boulder, CO), has been developed and proposed to predict response to TKIs. The test relies on a predictive algorithm based on matrix-assisted laser desorption ionization (MALDI) mass spectrometry (MS) analysis of pretreatment serum to generate a “good” or “poor” assessment for response to TKIs. VeriStrat has been proposed as a method to predict response to erlotinib in patients with NSCLC after failure of treatment with first-line therapy. Proposed uses have been in addition to EGFR testing, or in patients who do not have tumor samples available for EGFR testing.

Although the VeriStrat MALDI-MS-based predictive algorithm has the largest body of literature associated with it, other investigators have used alternative MS methods, such as surface-enhanced laser desorption ionization/time-of-flight MS, and alternative predictive algorithms, in the assessment of proteomic predictors of lung cancer risk.

**Summary of Evidence**

For individuals with epidermal growth factor receptor (EGFR)-negative or EGFR-status unknown non-small cell lung cancer (NSCLC) with disease progression after first-line treatment who receive management with a serum proteomic test to select targeted therapy, the evidence includes 1 prospective study evaluating the test’s use in predicting response to EGFR tyrosine kinase inhibitor (TKI) therapy and retrospective studies evaluating the prognostic ability of this test. Relevant outcomes are overall survival and disease-specific survival. Although a limited body of evidence exists for the analytic validity of proteomic testing to predict response to EGFR TKIs for NSCLC in general, at least 1 study has reported good test reproducibility for the most widely studied proteomic test, the VeriStrat assay. Evidence from retrospective studies has supported the clinical validity of proteomic testing in determining the prognosis of patients with advanced NSCLC who are treated with EGFR TKIs, but, due to heterogeneity in the treatment regimens used, it is difficult to determine specific populations for whom proteomic testing is prognostic. Evidence from 1 prospective study found that VeriStrat discriminates between patients who are likely to respond to EGFR-TKI therapy. However, in that same study, even those patients who were predicted to respond to EGFR-TKI therapy did not have a significant survival benefit with EGFR-TKI therapy. If EGFR-TKI therapy were used as a standard of care in patients who are EGFR-unknown or -negative in the second- or third-line setting, proteomic testing could be used to select patients who are least likely to benefit, and those patients could be offered chemotherapy as an alternative. RCT evidence has suggested that erlotinib is not beneficial for EGFR-unknown or -negative patients in the second-line setting, and clinical guidelines do not support its use. 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 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>
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<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02055144</td>
<td>VeriStrat as Predictor of Benefit of First Line Non-Small Cell Lung Cancer (NSCLC) Patients From Standard Chemotherapy</td>
<td>100</td>
<td>May 2015 (ongoing)</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01652469*</td>
<td>Testing of Drugs Erlotinib and Docetaxel in Lung Cancer Patients Classified Regarding Their Outlook Using VeriStrat® (EMPHASIS)</td>
<td>500</td>
<td>Dec 2015 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored 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, input was received from 1 academic medical center and 2 community health systems, one of which provided 4 responses, while this policy was under review in 2017. Input was uniform that erlotinib is not considered routine for individuals with non-small cell lung cancer (NSCLC) who are EGFR-negative or EGFR-status unknown in the second-line setting. Reviewers had limited confidence that there is adequate evidence that the use of VeriStrat to guide treatment selection will improve outcomes for individuals with NSCLC who are EGFR-negative or EGFR-status unknown in the second-line setting.
Practice Guidelines and Position Statements

**American College of Chest Physicians**

American College of Chest Physicians (ACCP) updated its evidence-based clinical practice guidelines on the treatment of stage IV NSCLC in 2013. Based on a review of the literature, ACCP reported improved response rates, progression-free survival, and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with EGFR variants, especially exon 19 deletion and L858R. ACCP recommended “testing patients with NSCLC for EGFR variants at the time of diagnosis whenever feasible, and treating with first-line EGFR TKIs if mutation-positive.”

**American Society of Clinical Oncology**

In 2011, the American Society of Clinical Oncology (ASCO) issued a provisional clinical opinion on EGFR mutation testing for patients with advanced NSCLC who are considering first-line EGFR TKI therapy. The authors concluded that such patients who have not previously received chemotherapy or an EGFR TKI should undergo EGFR mutation testing to determine whether chemotherapy or an EGFR TKI is appropriate first-line treatment.

In 2015, ASCO issued a clinical practice guideline update on systemic therapy for stage IV NSCLC, which makes the following recommendations about EGFR TKI therapy as second- or third-line treatment in patients without a sensitizing EGFR mutation:

- For second-line treatment, for patients with nonsquamous-NSCLC, docetaxel, erlotinib, gefitinib, or pemetrexed are acceptable (evidence quality: high; strength of recommendation: strong).
- For third-line treatment, for patients who have not received erlotinib or gefitinib and have performance status 0-3, erlotinib may be recommended.

**College of American Pathologists et al.**

In 2013, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR TKI therapy.
Based on excellent quality evidence (category A), the guidelines recommend EGFR mutation testing in patients with lung adenocarcinoma regardless of clinical characteristics, such as smoking history.

**EGFR-Negative or –Unknown Populations**

For patients with advanced nonsquamous NSCLC who are PD-L1- and ROS1-negative or -unknown, and without ALK rearrangements or sensitizing EGFR variants, systemic chemotherapy is recommended.

For patients with advanced nonsquamous NSCLC who are PD-L1-, ROS1-, and EGFR1-negative or -unknown, and without ALK rearrangements, who have progression on first-line systemic chemotherapy, with good performance status, treatment options include the following:

- Systemic immune checkpoint inhibitors (preferred):
  - Nivolumab (category 1 recommendation); OR
  - Pembrolizumab (category 1 recommendation); OR
  - Atezolizumab (category 1 recommendation); OR

- Other systemic therapy:
  - Docetaxel; OR
  - Pemetrexed; OR
  - Gemcitabine; OR
  - Ramucirumab and Docetaxel.

**EGFR-Positive Populations**

Erlotinib, afatinib, or gefitinib are recommended as first-line therapy for patients with advanced or metastatic NSCLC with sensitizing EGFR variants (category 1 recommendation). If the variant is discovered during first-line chemotherapy, NCCN recommends completing planned chemotherapy, including maintenance therapy, or interrupting followed by erlotinib, afatinib, or gefitinib.
For EGFR-positive patients who have progression on a tyrosine kinase inhibitor (TKI), T790M testing is recommended. Treatment options following progression include local therapy, osimertinib (if T790M-positive; category 1 recommendation), or continuation of erlotinib, afatinib, or gefitinib, depending on the level and location of symptoms.

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network guidelines on the management of non-small cell lung cancer (NSCLC; v.4.2017) recommend routine testing for epidermal growth factor receptor (EGFR) variants in patients with metastatic nonsquamous NSCLC (category 1 recommendation) and consideration for EGFR variant testing in patients with metastatic squamous NSCLC who were never smokers or with small biopsy specimens or mixed histology (category 2A recommendation).

**Medicare National Coverage**

Novitas Solutions established a local Medicare coverage determination for the VeriStrat in June 2013, which serves as a national coverage determination because the test is only offered at a single lab within the local carrier’s coverage region. The coverage determination document notes that “The VeriStrat® assay (NOC 84999) is a mass spectrophotometric, serum-based predictive proteomics assay for NSCLC patients, where ‘first line’ EGFR mutation testing is either wild-type or not able to be tested (eg, if tissue might not be available).”

**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 Act (CLIA). The commercially available proteomic test, the VeriStrat test, 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>
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<tr>
<th>Date</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>01/13/15</td>
<td>New Policy. Policy created with literature review through September 6, 2014. Proteomic testing considered investigational for all indications in the management of non-small-cell lung cancer.</td>
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<tr>
<td>01/19/16</td>
<td>Coding update. New CPT code 81538, effective 1/1/16, added to policy.</td>
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<tr>
<td>05/01/17</td>
<td>Annual Review, changes approved April 11, 2017. Policy updated with results of clinical input; reference 10 added. Policy statement unchanged. The term mutations replaced with the term variants.</td>
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<tr>
<td>10/24/17</td>
<td>Policy moved to new format; no change to policy statements.</td>
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Email AppealsDepartmentinquines@Premera.com

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 Arabic (Arabic):

يحيى هذا الإشعار معلومات هامة. قد يحيى هذا الإشعار معلومات هامة بخصوص تلك أو تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصول عليها من خلال هذا الإشعار. قد يحوي هذا الإشعار معلومات هامة بخصوص تلك المعلومة التي تيدر الحصل