### Introduction

A pulmonary nodule is a growth in the lung. Finding out if a nodule is benign (not harmful) or malignant (cancerous) often involves taking a sample of the nodule. Getting this sample requires an invasive procedure (invasive means something is put into the body). Depending on where the nodule is, the sample can be collected by passing a needle through the skin and chest wall into the lung, or using a viewing instrument called a bronchoscope that’s passed down the throat and into the lung’s airways. When there is a strong suspicion of cancer, surgery can also be used to remove the nodule, and a sample is then examined to determine if cancer is present.

Recently, tests have been developed that look at certain levels of proteins in the blood. The goal is to try to determine if invasive testing is needed for pulmonary nodules. These protein tests are investigational (unproven). More study is needed to determine if these tests are effective.

---

**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

Service | Investigational
--- | ---
Plasma-based proteomic screening | Plasma-based proteomic testing, including but not limited to BDX-XL2, in patients with undiagnosed pulmonary nodules detected by computed tomography is considered investigational.

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>0080U</td>
<td>Oncology (Lung), Mass Spectrometric Analysis of Galectin-3-Binding Protein And Scavenger Receptor Cysteine-Rich Type 1 Protein M130, With Five Clinical Risk Factors (Age, Smoking Status, Nodule Diameter, Nodule-Spiculation Status and Nodule Location), Utilizing Plasma, Algorithm Reported as a Categorical Probability of Malignancy (BDX-XL2) (new code effective 1/1/19)</td>
</tr>
<tr>
<td>0092U</td>
<td>Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy (Reveal Lung Nodule Characterization) (new code effective 7/1/19)</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

Plasma-based proteomic screening of is a molecular test available in the diagnostic workup of pulmonary nodules. To rule out malignancy, invasive diagnostic procedures such as computed tomography (CT)-guided biopsies, bronchoscopies, or video-assisted thoracoscopic surgery are often required, but each carry procedure-related complications ranging from postprocedure pain to pneumothorax. Molecular diagnostic tests have been proposed to aid in risk-stratifying patients to eliminate or necessitate the need for subsequent invasive diagnostic procedures.

Background

**Pulmonary Nodules**

Pulmonary nodules are a common clinical problem that may be found incidentally on a chest x-ray or computed tomography (CT) scan or during lung cancer screening studies of smokers. The primary question after the detection of a pulmonary nodule is the probability of malignancy, with subsequent management of the nodule based on various factors such as the radiographic characteristics of the nodules (eg, size, shape, density) and patient factors (eg, age, smoking history, previous cancer history, family history, environmental/occupational exposures). The key challenge in the diagnostic workup for pulmonary nodules is appropriately ruling in patients for invasive diagnostic procedures and ruling out patients who should forgo invasive diagnostic procedures. However, due to the low positive predictive value of pulmonary nodules detected radiographically, many unnecessary invasive diagnostic procedures and/or surgeries are performed to confirm or eliminate the diagnosis of lung cancer.

**Proteomics**

Proteomics is the study of the structure and function of proteins. The study of the concentration, structure, and other characteristics of proteins in various bodily tissues, fluids, and other materials has been proposed as a method to identify and manage various diseases, including cancer. In proteomics, multiple test methods are used to study proteins. Immunoassays use antibodies to detect the concentration and/or structure of proteins. Mass spectrometry is an analytic technique that ionizes proteins into smaller fragments and determines mass and composition to identify and characterize them.
Plasma-Based Proteomic Screening for Pulmonary Nodules

Plasma-based proteomic screening has been investigated to risk-stratify pulmonary nodules as likely benign to increase the number of patients who undergo serial CT scans of their nodules (active surveillance), instead of invasive procedures such as CT-guided biopsy or surgery. Additionally, proteomic testing may also determine a likely malignancy in clinically low-risk or intermediate-risk pulmonary nodules, thereby permitting earlier detection in a subset of patients.

Xpresys Lung and BDX-XL2 are plasma-based proteomic screening tests that measure the relative abundance of proteins from multiple disease pathways associated with lung cancer using an analytic technique called multiple reaction monitoring mass spectroscopy. The role of the tests is to aid physicians in differentiating likely benign from likely malignant nodules. If the test yields a likely benign result, patients may choose active surveillance via serial CT scans to monitor the pulmonary nodule. If the test yields a likely malignant result, invasive diagnostic procedures would be indicated. The test is therefore only used in the management of pulmonary nodules to rule in or out invasive diagnostic procedures and does not diagnose lung cancer.

Summary of Evidence

For individuals with undiagnosed pulmonary nodules detected by computed tomography (CT) who receive plasma-based proteomic screening, the evidence includes prospective cohorts and prospective-retrospective studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, hospitalizations, and resource utilization. Clinical validation studies were identified for two versions of a proteomic classifier. This classifier has undergone substantial evolution, from a 13 protein assay to a 2 protein assay integrated with clinical factors. Because of this evolution, the most relevant studies are with the most recent version two. One validation study on the version two has been identified. The classifier has been designed to have high specificity for malignant pulmonary nodules, and the validation study showed a specificity of 97% for patients with low to moderate pretest probability (< 50%) of a malignant pulmonary nodule. The primary limitation of this study is that a high number of patients were excluded from the study due to incomplete clinical data or because they were subsequently determined to be outside of the intended use population. It is unclear if the intended use population was determined a priori. Validation in an independent sample in the intended use population is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.
Ongoing and Unpublished Clinical Trials

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

Practice Guidelines and Position Statements

American College of Chest Physicians

The American College of Chest Physicians (2013) has published evidence-based clinical practice guidelines on the diagnosis and management of lung cancer, including pulmonary nodules, which is discussed in the patient population parameters in the Plasma-Based Proteomic Screening of Pulmonary Nodules section.12

American Thoracic Society

The American Thoracic Society (2017) published a position statement on the evaluation of molecular biomarkers for the early detection of lung cancer.5 The Society states that “a clinically useful molecular biomarker applied to the evaluation of lung nodules may lead to expedited therapy for early lung cancer and/or fewer aggressive interventions in patients with benign lung nodules.” To be considered clinically useful, a molecular diagnosis “must lead to earlier diagnosis of malignant nodules without substantially increasing the number of procedures performed on patients with benign nodules” or “fewer procedures for patients with benign nodules without substantially delaying the diagnosis of cancer in patients with malignant nodules.”

Medicare National Coverage

MolDX will provide limited coverage for the BDX-XL2 test (Biodesix) for the management of a lung nodule between 8 and 30mm in diameter, in patients at least 40 years of age and with a pre-test cancer risk of 50% or less, as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules.
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. Xpresys® Lung 2 (BDX-XL2 (Integrated Diagnostics [Indi], purchased by Biodesix) Reveal Lung Nodule Characterization (MagArray 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

History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/04/19</td>
<td>New policy, approved December 13, 2018, effective January 4, 2019. This policy replaces policy 12.04.142. Percepta® Bronchial Genomic Classifier removed from policy.</td>
</tr>
<tr>
<td>05/01/19</td>
<td>Minor update, History section updated for clarity.</td>
</tr>
<tr>
<td>08/01/19</td>
<td>Annual Review, approved July 25, 2019. Policy updated with literature review through March 2019; references added. Name of proteomic plasma assay changed to BDX-XL2. Removed CPT code 84999. Added CPT codes 0080U (new code effective 1/1/19) and 0092U (new code effective 7/1/19).</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). ©2019 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.

Getting Help in Other Languages

This Notice has Important Information. If you communicate in Spanish, you have the right to get this information and help in your language at no cost.

Premera Blue Cross. If you need help filing a grievance or if you believe that Premera Blue Cross 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
200 Independence Avenue SW, Room 509F, HHH Building
U.S. Department of Health and Human Services
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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.

Getting Help in Other Languages

This Notice has Important Information. If you communicate in Spanish, you have the right to get this information and help in your language at no cost.

Premera Blue Cross. If you need help filing a grievance or if you believe that Premera Blue Cross 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
200 Independence Avenue SW, Room 509F, HHH Building
U.S. Department of Health and Human Services
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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.

Getting Help in Other Languages

This Notice has Important Information. If you communicate in Spanish, you have the right to get this information and help in your language at no cost.

Premera Blue Cross. If you need help filing a grievance or if you believe that Premera Blue Cross 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
200 Independence Avenue SW, Room 509F, HHH Building
U.S. Department of Health and Human Services
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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.

Getting Help in Other Languages

This Notice has Important Information. If you communicate in Spanish, you have the right to get this information and help in your language at no cost.

Premera Blue Cross. If you need help filing a grievance or if you believe that Premera Blue Cross 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
200 Independence Avenue SW, Room 509F, HHH Building
U.S. Department of Health and Human Services
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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.
Talvez seja necessário que você tome providências dentro de 800-722-1471 (TTY: 800-842-5357) ou entre em contato com a nossa equipe de atendimento.

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica a un costo. Usted tiene derecho a recibir esta información en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).