Molecular Testing in the Management of Pulmonary Nodules

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 and changes within genes. The goal is to try to determine if invasive testing is needed for pulmonary nodules. These protein and genetic 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

<table>
<thead>
<tr>
<th>Service</th>
<th>Investigational</th>
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<tbody>
<tr>
<td>Plasma-based proteomic screening</td>
<td>Plasma-based proteomic testing, including but not limited to Xpresys® Lung, of patients with unbiopsied pulmonary nodules that were detected radiographically is considered investigational.</td>
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<tr>
<td>Gene expression profiling</td>
<td>Gene expression profiling on bronchial brushings, including but not limited to Percepta® Bronchial Genomic Classifier, taken from patients with pulmonary nodules who have indeterminate bronchoscopy results is considered investigational.</td>
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### Coding

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<th>Code</th>
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<td>CPT</td>
<td>Unlisted chemistry procedure</td>
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## Related Information

N/A

## Evidence Review
Description

Plasma-based proteomic screening and gene expression profiling of bronchial brushing are molecular tests 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 carries 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, computed tomography (CT) scan, or during lung cancer screening studies of smokers. The primary question after the detection of a pulmonary nodule is whether it is malignant. The subsequent management of the nodule depends 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 concentration, structure and other characteristics of proteins in various locations of the body has been proposed as a way to identify and manage various diseases, including cancer. Many test methods have been used to study proteins. For example, immunoassays use antibodies to detect the concentration and/or structure of proteins, while mass spectrometry ionizes proteins into smaller fragments and determines their mass and composition in order to identify and characterize them.
Plasma-Based Proteomic Screening for Pulmonary Nodules

Plasma-based proteomic screening has been investigated as a means to risk-stratify pulmonary nodules. If a nodule is felt to likely be benign, a patient may be able to safely have serial CT scans of their nodules (active surveillance) instead of undergoing invasive procedures such as CT-guided biopsy or surgery. Additionally, proteomic testing may help determine that a clinically low-risk or intermediate-risk pulmonary nodule is likely malignant, thereby permitting earlier detection and treatment in a subset of patients.

Xpresys Lung is a plasma-based proteomic screening test that measures 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 test is to aid physicians in differentiating nodules that are likely benign from those that are likely malignant. If the test shows a nodule to be likely benign, patients may choose active surveillance by way of serial CT scans to monitor the pulmonary nodule. However, if the test shows a nodule to be likely malignant, 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 is not used to diagnose lung cancer.

Gene Expression Profiling

Gene expression profiling measures the activity of genes within cells. It can be used on clinical samples to look for cancer-associated gene expression patterns that are common in malignancy.

Gene Expression Profiling for an Indeterminate Bronchoscopy Result

The Percepta Bronchial Genomic Classifier is a 23-gene gene expression profiling test that analyzes genomic changes in the airways of current or former smokers to assess a patient’s risk of having lung cancer, without the direct testing of a pulmonary nodule. The test is indicated for current and former smokers following an indeterminate bronchoscopy result to determine subsequent management of pulmonary nodules (eg, active surveillance or 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 an analytic validity study as well as prospective cohort and prospective-retrospective studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, hospitalizations, and resource utilization. The commercially available tests have been designed to have a high negative predictive value (NPV) of 90%, although studies have reported on slightly different versions. A single multicenter prospective-retrospective study revealed that 32% of surgeries and 31.8% of invasive procedures could have been avoided. However, 24.0% of patients with malignancy would have been triaged to CT surveillance (false-negative). Studies have not reported how it reclassifies patients relative to clinical classifiers in terms of risk. Indirect evidence has suggested that a proteomic classifier with high NPV has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with unbiopsied pulmonary nodules who had an inconclusive bronchoscopy and then had gene expression profiling done on their bronchial brushings, the evidence includes an analytic study and multicenter prospective studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, hospitalizations, and resource utilization. Reported receiver operating characteristic curve values ranged from 0.74 to 0.81, with a NPV of 91%. Among patients with low and intermediate pretest probability of cancer with an inconclusive bronchoscopy, 77 (85%) patients underwent invasive diagnostic procedures. However, there were a relatively high number of missed cancers. No validation of the test in other populations was identified. In addition, where the test would fall in the clinical pathway (ie, other than indeterminate bronchoscopy) is uncertain. 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 2017 did not identify any ongoing or unpublished trials that would likely influence this review.
Practice Guidelines and Position Statements

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.\textsuperscript{12}

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 (CLIA). Xpresys® Lung (Indi, Seattle, WA) and Percepta® Bronchial Genomic Classifier (Veracyte, South San Francisco, CA) are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests 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

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<th>Comments</th>
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<tr>
<td>08/01/17</td>
<td>New Policy, approved July 18, 2017. Policy created with literature review through March 30, 2017. Plasma-based proteomic screening including but not limited to Xpresys® Lung in patients with pulmonary nodules detected radiographically is considered investigational; Gene expression profiling on bronchial brushings including but not limited to Percepta® Bronchial Genomic Classifier in patients with indeterminate bronchoscopy results is considered investigational.</td>
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200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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