MEDICAL POLICY – 2.04.515
Plasma-based Proteomic Screening in the Management of Pulmonary Nodules

BCBSA Ref. Policy: 2.04.142
Effective Date: Jan. 4, 2019
Last Revised: May 1, 2019
Replaces: 12.04.142

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POLICY CRITERIA | CODING | RELATED INFORMATION
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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 test 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 Xpresys® Lung, in patients with undiagnosed pulmonary nodules detected by computed tomography is considered investigational.

Coding

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Related Information

N/A

Evidence Review

Description

Plasma-based proteomic screening of bronchial brushings 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 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 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 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 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 who receive plasma-based proteomic screening, the evidence includes a 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 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 computed tomography surveillance (false-negative). Studies have not reported how this proteomic screening reclassifies patients relative to clinical classifiers in terms of risk. Indirect evidence has suggested that a proteomic classifier with high negative predictive value 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.

**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

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.11

Medicare National Coverage

There is no national coverage determination.

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 (Indi) is available under the auspices of 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


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<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>
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<td>05/01/19</td>
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