Molecular Testing in the Management of Pulmonary Nodules

Policy # 00562
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers plasma-based proteomic screening, including but not limited to BDX-XL2 and REVEAL Lung Nodule Characterization, in patients with undiagnosed pulmonary nodules detected by computed tomography to be **investigational.***

Based on review of available data, the Company considers gene expression profiling on bronchial brushings, including but not limited to Percepta®‡ Bronchial Genomic Classifier, in patients with indeterminate bronchoscopy results from undiagnosed pulmonary nodules to be **investigational.***

Background/Overview

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.

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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.

Gene Expression Profiling
Gene expression profiling (GEP) is the measurement of the activity of genes within cells. Messenger RNA serves as the bridge between DNA and functional proteins. Multiple molecular techniques such as Northern blots, ribonuclease protection assay, in situ hybridization, spotted complementary DNA arrays, oligonucleotide arrays, reverse transcriptase polymerase chain reaction, and transcriptome sequencing are used in GEP. An important role of GEP in molecular diagnostics is to detect cancer-associated gene expression of clinical samples to assess for the risk for malignancy.

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Gene Expression Profiling for an Indeterminate Bronchoscopy Result
The Percepta Bronchial Genomic Classifier is a 23-gene, GEP 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 the subsequent management of pulmonary nodules (eg, active surveillance or invasive diagnostic procedures), and does not diagnose lung cancer.

REVEAL Lung Nodule Characterization (MagArray) is a plasma protein biomarker test that may aid clinicians in characterizing indeterminate pulmonary nodules (4-30 mm) in current smokers aged 25 years and older. The test uses immunoassay, microarray, and magnetic nanoparticle detection techniques. The REVEAL Lung Nodule Characterization score is presented on a scale from 0 to 100 with a single cut point at 50, and the score is calculated using an algorithm based on the measurement of 3 clinical factors (smoking history, patient age, nodule size) and 3 blood proteins (epidermal growth factor receptor [EGFR], prosurfactant protein B (ProSB), tissue inhibitor of metalloproteinases 1 (TIMP1) associated with the presence of lung cancer. This result may aid in the decision to perform a biopsy, or to consider routine monitoring.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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 2 (BDX-XL2 (Integrated Diagnostics [Indi], purchased by Biodesix) and Percepta®‡ Bronchial Genomic Classifier (Veracyte) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

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-guided biopsies, bronchoscopies, or video-assisted thoracoscopic procedures are often required, but each carry procedure-related

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complications ranging from post procedure 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.

For individuals with undiagnosed pulmonary nodules detected by computed tomography 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 2 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 2. One validation study on version 2 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.

While the REVEAL biomarker assay has shown promising results in differentiating malignant from benign lesions, further research is needed to more broadly assess the impact of the test on clinical decision making. Ideally long-term follow-up including the rate of lung cancer deaths prevented using this test is desired to further verify this as an effective risk assessment of lung cancer. This plasma-protein signature should also be more directly assessed in all races, as well as specific conditions such as obesity and its pro-inflammatory state, steroid use, etc., that may affect the test performance. Further clinical studies are warranted to define the value of the test in accurately identifying patients who are most likely to benefit from serial surveillance or early treatment, while reducing the rate of false-positive results, unnecessary interventions, and their associated morbidity and healthcare costs.

For individuals with undiagnosed pulmonary nodules following indeterminate bronchoscopy results for suspected lung cancer who receive gene expression profiling of bronchial brushings, the evidence includes multicenter prospective studies. Relevant outcomes are overall survival, disease-specific

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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 negative predictive value of 91%. Among patients with a low and intermediate pretest probability of cancer with an inconclusive bronchoscopy, 77 (85%) patients underwent invasive diagnostic procedures. However, there was a relatively high number of missed cancers. No validation of the test in other populations was identified. Also, 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.

Supplemental Information

Practice Guidelines and Position Statements

American College of Chest Physicians

In 2013, the American College of Chest Physicians 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.

American Thoracic Society

In 2017, the American Thoracic Society published a position statement on the evaluation of molecular biomarkers for the early detection of lung cancer. 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."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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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.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in March 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

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08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. New policy.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. No change to coverage.
06/10/2019	Coding update
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. New Assay was added to policy changing name of proteomic plasma assay from Xpresys to BDX- XL2.
08/06/2020	Medical Policy Committee review

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Code Type	Code
CPT	0019U, 0080U, 0092U, 81479, 83520, 84999
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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