Medical Coverage Policy | Molecular Testing in the Management of Pulmonary Nodules

EFFECTIVE DATE: 04|01|2021
POLICY LAST UPDATED: 12|02|2020

OVERVIEW

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 are often required, but each carry procedure-related 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.

The following tests are addressed in this policy:

- Xpresys® Lung 2 (BDX-XL2 (Integrated Diagnostics)
- Percepta® Bronchial Genomic Classifier (Veracyte)
- REVEAL Lung Nodule Characterization (MagArray)

MEDICAL CRITERIA

Medicare Advantage Plans

Percepta (81479)

Gene expression profiling on bronchial brushings not limited to Percepta is medically necessary when all the criteria ae met

• Current or former smokers age 21 and greater, **and**

• Physician-assessed low or intermediate pretest risk of malignancy based upon the following clinical characteristic stratification, **and:**

Low Risk (<10%)	**Intermediate Risk (10-60%)**	**High Risk (>60%)**
Nodules < 10 mm <10 pk/yr smoking history	Nodules 10 - 30 mm 10 to 60 pk/yr smoking history	Nodules >30 mm >60 pk/yr smoking history

• Bronchoscopy is non-diagnostic (actionable benign or malignant diagnosis cannot be reached), **and**

• **PERCEPTA** BGC results will be utilized to determine whether CT surveillance is appropriate in lieu of further invasive biopsies or surgical procedures

Xpresys® Lung 2 BDX-XL2 (0080U) and REVEAL Lung Nodule Characterization (0092U)

Plasma-based proteomic screening not limited to BDX-XL2 and REVEAL Lung Nodule Characterization may be considered medically necessary when the BlueCHiP for Medicare medical necessity criteria is used for review. The criteria can be found in the Medical Necessity policy. Please see Related Policies section.

PRIOR AUTHORIZATION

Medicare Advantage Plans

Prior Authorization is required for only for the following tests:

- Xpresys® Lung 2 (BDX-XL2 (Integrated Diagnostics)
- Percepta® Bronchial Genomic Classifier (Veracyte)

- REVEAL Lung Nodule Characterization (MagArray)

Commercial Products
Not applicable

POLICY STATEMENT

Medicare Advantage Plans
The following tests may be medically necessary when the medical criteria are met.

- Xpresys® Lung 2 (BDX-XL2 (Integrated Diagnostics)
- Percepta® Bronchial Genomic Classifier (Veracyte)
- REVEAL Lung Nodule Characterization (MagArray)

Commercial Products
The following tests are not medically necessary as evidence is insufficient to determine the effects of the technology on health outcomes:

- Xpresys® Lung 2 (BDX-XL2 (Integrated Diagnostics)
- Percepta® Bronchial Genomic Classifier (Veracyte)
- REVEAL Lung Nodule Characterization (MagArray)

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not covered/medically necessary.

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.

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.

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.

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 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. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Commercial Products

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 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.

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.

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 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.

Medicare Advantage Plans
PERCEPTA™ Bronchial Genomic Classifier (PERCEPTA BGC) Test Description and Performance
The **PERCEPTA** BGC is a messenger-RNA assay measuring gene expression of 23 lung cancer associated genes and patient age. The assay is performed on cytology brushings of bronchial epithelial cells collected during a bronchoscopy from the main stem bronchus and stored in an RNA preservative at 4°C immediately after collection. The assay results are reported as a categorical result based on the patient's physician-assessed pretest risk of malignancy as described below.

Table 2: **PERCEPTA** Classifier Results

Pre-Test	**Post Test Risk of Malignancy**	
Pretest Risk of Malignancy	**PERCEPTA Negative Result**	**PERCEPTA Positive Result**
Low (<10%)	Very Low (<1%)	Low (<10%)

CODING

The following codes are covered for **Medicare Advantage Plans** when the criteria are met and not medically necessary for Commercial Products:
Xpresys® Lung 2BDX-XL2
0080U 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

REVEAL Lung Nodule Characterization
0092U Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy (**REVEAL Lung Nodule Characterization**)

PERCEPTA
There is no specific CPT for **Percepta** therefore, claims should be filed with the following unlisted code:
81479 Unlisted molecular pathology procedure

RELATED POLICIES

Unlisted Services
Genetic Testing
Medical Necessity

PUBLISHED

Provider Update, February 2021
Provider Update, December 2020
Provider Update, November 2019

Provider Update, October 2018
Provider Update, October 2017

REFERENCES:

1. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. May 2013; 143(5 Suppl): e93S-e120S. PMID 23649456
2. Li XJ, Hayward C, Fong PY, et al. A blood-based proteomic classifier for the molecular characterization of pulmonary nodules. Sci Transl Med. Oct 16 2013; 5(207): 207ra142. PMID 24132637
3. Vachani A, Pass HI, Rom WN, et al. Validation of a multiprotein plasma classifier to identify benign lung nodules. J Thorac Oncol. Apr 2015; 10(4): 629-37. PMID 25590604
4. Vachani A, Hammoud Z, Springmeyer S, et al. Clinical Utility of a Plasma Protein Classifier for Indeterminate Lung Nodules. Lung. Dec 2015; 193(6): 1023-7. PMID 26376647
5. Kearney P, Hunsucker SW, Li XJ, et al. An integrated risk predictor for pulmonary nodules. PLoS ONE. 2017; 12(5): e0177635. PMID 28545097
6. Silvestri GA, Tanner NT, Kearney P, et al. Assessment of Plasma Proteomics Biomarker's Ability to Distinguish Benign From Malignant Lung Nodules: Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial. Chest. Sep 2018; 154(3): 491-500. PMID 29496499
7. Vachani A, Pass HI, Rom Wn, et al. Validation of a multiprotein plasma classifier to identify benign lung nodules. Supplement. J Thorac Oncol. April 2015;10(4):629-637. https://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/JTO/A/JTO_10_4_2015_01_07_MASSION_JTO-D-14-00912_SDC1.pdf. Accessed March 19, 2020.
8. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. May 2013; 143(5 Suppl): e142S-e165S. PMID 23649436
9. Whitney DH, Elashoff MR, Porta-Smith K, et al. Derivation of a bronchial genomic classifier for lung cancer in a prospective study of patients undergoing diagnostic bronchoscopy. BMC Med Genomics. May 06 2015; 8: 18. PMID 25944280
10. Silvestri GA, Vachani A, Whitney D, et al. A Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer. N Engl J Med. Jul 16 2015; 373(3): 243-51. PMID 25981554
11. Vachani A, Whitney DH, Parsons EC, et al. Clinical Utility of a Bronchial Genomic Classifier in Patients With Suspected Lung Cancer. Chest. Jul 2016; 150(1): 210-8. PMID 26896702
12. Ferguson JS, Van Wert R, Choi Y, et al. Impact of a bronchial genomic classifier on clinical decision making in patients undergoing diagnostic evaluation for lung cancer. BMC Pulm Med. May 17 2016; 16(1): 66. PMID 27184093
13. Detterbeck FC, Lewis SZ, Diekemper R, et al. Executive Summary: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. May 2013; 143(5 Suppl): 7S-37S. PMID 23649434
14. Mazzone PJ, Sears CR, Arenberg DA, et al. Evaluating Molecular Biomarkers for the Early Detection of Lung Cancer: When Is a Biomarker Ready for Clinical Use? An Official American Thoracic Society Policy Statement. Am J Respir Crit Care Med. Oct 01 2017; 196(7): e15-e29. PMID 28960111

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