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

EFFECTIVE DATE: 01|01|2024
POLICY LAST UPDATED: 10|02|2023

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:

- Nodify XL2 (BDX-XL2) (Biodesix®, Inc) (CPT code 0080U)
- Percepta® Bronchial Genomic Classifier (Veracyte) (CPT code 81479)
- REVEAL Lung Nodule Characterization (MagArray) (CPT code 0092U)
- Nodify CDT® (Biodesix®, Inc) (CPT code 0360U)

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

Percepta (CPT code 81479)

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

PRIOR AUTHORIZATION

Prior Authorization is required for the Percepta® Bronchial Genomic Classifier (Veracyte) test for Medicare Advantage Plans and is recommended for Commercial Products.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The Percepta® Bronchial Genomic Classifier (Veracyte) may be medically necessary when the medical criteria are met.

The following tests are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- Nodify XL2 (BDX-XL2) (Biodesix®, Inc)
- REVEAL Lung Nodule Characterization (MagArray)
- Nodify CDT® Biodesix®, Inc

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. **§27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

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 (e.g., size, shape, density) and patient factors (e.g., 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.

Nodify XL2 (BDX-XL2) 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 test helps physicians identify lung nodules that are likely

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benign or at lower risk of cancer. If the test yields a "likely benign" or "reduced risk" result, patients may choose active surveillance via serial CT scans to monitor the pulmonary nodule. Earlier generations of the Nodify XL2 test include Xpresys Lung® and Xpresys Lung 2®.

Nodify CDT® is a proteomic test that uses multi-analyte immunoassay technology to measure autoantibodies associated with tumor antigens. The test helps physicians identify lung nodules that are likely malignant or at higher risk of cancer. Patients with a "high level" Nodify CDT test result have a higher risk of malignancy than predicted by clinical factors alone; invasive diagnostic procedures would be indicated in these cases.

The Nodify XL2 and Nodify CDT tests are therefore only used in the management of pulmonary nodules to rule out or rule in, invasive diagnostic procedures; they do not diagnose lung cancer. These tests are offered together as Biodesix's Nodify Lung® testing strategy, but physicians may also choose to order each test independently.

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 first generation Percepta® Bronchial Genomic Classifier was a 23-gene, GEP test that analyzed 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. This classifier was designed to be a "rule-out" test for intermediate-riskpatients. The second generation Percepta Genomic Sequencing Classifier was developed to serve as both a"rule-in" test and a "rule-out" test, thereby increasing its potential utility in improving risk stratification. The test is indicated for current and former smokers following an indeterminate bronchoscopy result to determine the subsequent management of pulmonary nodules (e.g., 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, now Nodify XL2 (BDX-XL2; Integrated Diagnostics [Indi], purchased by Biodesix); Nodify CDT (Biodesix) and Percepta® Genomic Sequencing 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.

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 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,

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hospitalizations, and resource utilization. Clinical validation studies were identified for 2 versions (XpresysLung, and Xpresys Lung version 2 [now Nodify XL2]) 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 (Xpresys Lung version 2 [now Nodify XL2]). 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. No recent clinical validation studies were identified for the Nodify CDT test or the Nodify Lung testing strategy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

The Percepta Bronchial Genomic Classifier 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%)
Intermediate (10-65%)	Low (<10%)	Intermediate (10-65%)
High (>65%)	High (>65%)	Very High (>85%)

The usefulness of the assay in the low and intermediate pretest risk groups has been evaluated in two additional modeling studies13. These studies suggest that use of the classifier may safely reduce invasive surgical procedures among patients with a low or intermediate pretest risk following a non-diagnostic bronchoscopy. Veracyte is also currently running the PERCEPTA Registry Trial to prospectively evaluate the clinical utility of the classifier.

The potential usefulness of this test is that it allows physicians to determine which patients with a low or intermediate physician-assessed pretest risk and a non-diagnostic bronchoscopy may be candidates for CT surveillance in lieu of further invasive biopsies or surgical procedures.

CODING

The following code(s) are covered for Medicare Advantage Plans and Commercial Products when the medical criteria above is met:

Percepta® Bronchial Genomic Classifier

There is no specific CPT for Percepta®**.** Therefore, claims should be filed with the following unlisted code:

81479 Unlisted molecular pathology procedure

The following code(s) are not covered for Medicare Advantage Plans and are not medically necessary for Commercial Products:

Nodify XL2 (**BDX-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

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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**)

Nodify CDT®

0360U Oncology (lung), enzyme-linked immunosorbent assay (ELISA) of 7 autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, MAGE A4, and HuD), plasma, algorithm reported as a categorical result for risk of malignancy (Nodify CDT® Biodesix, Inc.) **(New Code Effective 4/1/2023)**

RELATED POLICIES

Biomarker Testing Mandate
Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations
Genetic Testing Services
Proprietary Laboratory Analysis (PLA)
Unlisted Procedures

PUBLISHED

Provider Update, November 2023
Provider Update, October 2022
Provider Update, October 2021, February 2021
Provider Update, December 2020
Provider Update, November 2019

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. Tanner NT, Springmeyer SC, Porter A, et al. Assessment of Integrated Classifier's Ability to Distinguish Benign From Malignant Lung Nodules: Extended Analyses and 2-Year Follow-Up Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial. Chest. Mar 2021; 159(3): 1283-1287. PMID 33171158
8. 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 April 1, 2022.
9. 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

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10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. National Comprehensive Cancer Network. NCCN Guidelines Version 2.2023: Non-Small Cell Lung Cancer. 2023; https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed March 13, 2023
17. National Comprehensive Cancer Network. NCCN Guidelines Version 3.2023: Small Cell Lung Cancer.2023; https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed March 12, 2023.
18. National Comprehensive Cancer Network. NCCN Guidelines Version 1.2023: Lung Cancer Screening.2023; https://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf. Accessed March 11,2023.
19. Biodesix. Nodify Lung: Lung Nodule Management. 2023; https://www.biodesix.com/our-tests/nodify-lung. Accessed March 13, 2023.

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