

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



EFFECTIVE DATE: 06|01|2024
POLICY LAST REVIEWED: 02|21|2024

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

Nodify XL2 (BDX-XL2) (CPT code 0080U)

The Nodify XL2 is considered medically necessary when ALL of the following criteria is met:

1. For the management of a lung nodule, between 8 and 30mm in diameter; and,
2. Member is 40 years or older; and,
3. Pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) is 50% or less; and,
4. When the intended use of the test is to assist physicians in the management of lung nodules by identifying those lung nodules with a high probability of being benign; and,
5. The lung nodules would be candidates for non-invasive computed tomography (CT) surveillance instead of invasive procedures.

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 and Nodify XL2 (BDX-XL2) 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) and Nodify XL2 (BDX-XL2) 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:

- 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 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-risk patients. 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, hospitalizations, and resource utilization. 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.

Nodify XL2 (BDX-XL2)

Current practice has been previously characterized,^{4,11} as well as, the potential clinical utility of an earlier version.⁵ The clinical utility of BDX-XL2 (Nodify XL2) is measured in terms of its potential to reduce unnecessary invasive procedures, such as biopsies and surgeries, on benign lung nodules while not significantly increasing the number of malignant lung nodules routed to CT surveillance, thereby delaying surgical resection. Assuming strict adherence to management recommendations based on assay results (i.e., active surveillance if “likely benign”), an earlier version of Xpresys® Lung demonstrated a potential 32% reduction in invasive procedures on benign lung nodules without increasing the number of malignant nodules routed to CT surveillance⁵ based on a retrospective analysis of a prospective observational study of lung nodule management (NCT01752101). Similarly, in the PANOPTIC study, the potential clinical utility of the current version of BDX-XL2 was assessed retrospectively. Specifically, if BDX-XL2 were used to guide lung management (and assuming a post-test probability of 98%), then invasive procedures on benign lung nodules would have been reduced 36% (CI: 22%-52%) with only 3% (CI: 0%-18%) of malignant nodules routed to CT surveillance (compared to 45% with current practice in the PANOPTIC study).

The evidence of clinical utility for the BDX-XL2 assay for individuals age 40 and older with an 8 to 30 mm lung nodule and a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of at least 50% is promising at the current time. Clinical Studies underway at this time are expected to demonstrate clinical utility. These studies are designed to show a statistically significant reduction in the number of benign lung nodules experiencing invasive procedures between a prospective group of patients managed by BDX-XL2 and a contemporaneous group not managed by BDX-XL2. A secondary end-point will show that the management of lung nodules by BDX-XL2 does not (i.e., is statistically non-inferior to) the number of malignant nodules routed to CT surveillance (determined at 1-year interval) as compared to current practice without BDX-XL2. Continued coverage for BDX-XL2 testing will be dependent on annual review of prospective data and peer-reviewed studies.

Percepta Bronchial Genomic Classifier

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:

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

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:

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® Bionodesix, Inc.) (**New Code Effective 1/1/2023**)

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, April 2024
Provider Update, November 2023
Provider Update, October 2022
Provider Update, October 2021, February 2021
Provider Update, December 2020

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