MEDICAL POLICY

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Medical Policy Title	**Molecular Testing in the Management of Pulmonary Nodules**
Policy Number	**2.02.58**
Current Effective Date	**October 16, 2025**
Next Review Date	**October 2026**

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Molecular testing in the management of undiagnosed pulmonary nodules by plasma-based proteomic screening, gene expression of bronchial brushings or nasal swab, and flow cytometry of sputum, are considered **investigational** in **ALL** circumstances including, but not limited to, the following tests:

A. CyPath Lung (0406U)

B. EarlyCDT Lung (83520)

C. LungLB (0317U)

D. Nodify CDT (0360U)

E. Nodify XL2, (including the following prior generations of this test: Xpresys Lung, Xpresys Lung 2 [BDX-XL2]) (0080U)

F. OncobiotaLUNG (0395U)

G. ReVeal Lung Nodule Characterization (0092U)

H. Protein Assays Utilizing Lung Cancer Analytes (PAULA's Test)

I. Percepta Genomic Sequencing Classifier

J. Percepta Nasal Swab

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

DESCRIPTION

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 a range of 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 forego 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.

Plasma-based proteomic screening, gene expression profiling of bronchial brushing or nasal swab, and flow cytometry analysis of sputum are molecular tests available for 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. Invasive procedures carry risk for complications ranging from post-procedure pain to pneumothorax. Molecular diagnostic tests have been proposed to aid in risk-stratifying patients to determine the need for subsequent invasive diagnostic procedures.

CyPath Lung, Precision Pathology

CyPath Lung is a non-invasive, sputum-based test for the early diagnosis of lung cancer. It uses a fully automated flow cytometric platform to analyze the cellular content of sputum for patients whose computed tomography (CT) results in a suspicious finding. Patients collect sputum at home over three days with the assistance of a patient coach. CyPath Lung test results stratify the patient into one of two risk groups. Those patients deemed “likely or very likely” to have cancer may benefit from aggressive intervention. Those “unlikely or very unlikely” to have a malignancy may continue imaging surveillance. CyPath Lung reveals the lung micro-environment by automated analysis of sputum using flow cytometry to characterize cell populations indicative of cancer in the lung. CyPath Lung labels a person’s sputum sample with fluorescent antibodies that uniquely identify different cell types and a fluorescent porphyrin called TCPP that preferentially binds to cancer cells and cancer-related cells. TCPP fluoresces a bright red color when attached to cancer cells and cancer-associated cells that are visible when the sample is run through a flow cytometer. CyPath Lung uses automated analysis that looks for pre-set parameters that are predictive of cancer, one of which is the presence of cells that

have taken up greater amounts of the TCPP porphyrin label. This test is intended for use after lung cancer screening to improve early-stage lung cancer diagnosis.

EarlyCDT Lung, Oncimmune

EarlyCDT-Lung is a serum-based test that measures autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4, and SOX2) associated with small cell and non-small cell lung cancer (NSCLC). Positive results are reported as 'positive-moderate' if at least one (1) of the seven (7) autoantibodies is elevated above a predetermined 'low' threshold, but all are below the 'high' threshold. If at least one (1) of the seven (7) autoantibodies is elevated above the 'high' predetermined threshold, the test is reported as 'positive-high'. EarlyCDT Lung is proposed as a 'rule-in' test to be used in addition to standard care for the detection of lung cancer. The estimated post-test risk is intended to help clinicians make decisions about further testing or intervention. High-risk individuals with a positive EarlyCDT-Lung would have additional testing such as a CT scan or the test would be used as a follow-up test for indeterminate lung nodules identified by CT.

LungLB, LungLife AI

The LungLB test is a 4-color fluorescence in-situ hybridization (FISH) assay employed to detect early circulating tumor cells (CTCs) from peripheral blood draw. This assay was developed as a FISH-based liquid biopsy test utilizing DNA FISH to validate identification of CTC to assist in the clinical assessment of individuals with indeterminate nodules suspicious for lung cancer. LungLB uses a predictive algorithm to generate an evaluation reported as a decreased or increased risk for lung cancer.

Nodify CDT, Biodesix

Nodify CDT test aims to detect early-stage lung cancer in an individual who is at moderate to high-risk. The test measures seven (7) autoantibodies (CAGE, GBU4-5, HuD, MAGE A4, NY-ESO-1, p53 and SOX-2) that are claimed to be associated with tumor antigens to help detect lung cancer. The test aims to help physicians identify lung nodules that are likely malignant or at higher risk of cancer. Invasive diagnostic procedures would be indicated for patients with a "high level" Nodify CDT test result.

Nodify XL2, Biodesix
(including prior generations of this test: Xpresys Lung, Xpresys Lung 2 [BDX-XL2])

Nodify XL2 test aims to identify those patients whose pulmonary nodules have a high likelihood of being benign, and those who may be better candidates for non-invasive computed tomography (CT) surveillance versus surgical resection. This test utilizes plasma and an integrated classifier that measures the ratio of two (2) proteins (LG3BP and C163A) combined with several clinical and radiological factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location) to report a categorical probability of malignancy.

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.

OncobiotaLUNG, Micronoma

OncobiotaLUNG is a blood test used to measure microbial DNA by NGS, carcinoembryonic antigen and osteopontin by immunoassay. It is purported to detect malignancy risk for lung nodules in early-stage disease by microbiome-driven, liquid biopsy assay and categorize nodules as being high-risk or low-risk.

ReVeal Lung Nodule Characterization, MagArray

ReVeal Lung Nodule Characterization is a plasma-based 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, individual 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 making the decision to perform a biopsy, or to consider routine monitoring. REVEAL Lung Nodule Characterization is a risk assessment tool, which is to be used only in conjunction with standard clinical assessments. The test is not intended to be a screening or stand-alone diagnostic assay.

Protein Assays Utilizing Lung Cancer Analytes (PAULA's Test), Genesys Biolabs

PAULA's Test is a biomarker blood test for lung cancer. It is for people at high-risk for lung cancer due to a long term smoking history. This test aims to provide a risk score for lung cancer by measuring serum levels of several cancer markers. These marker tests include CEA (carcinoembryonic antigen), CA 125 (carbohydrate antigen 125), CYFRA 21-1 (cytokeratin-19 fragment 21-1) and NY-ESO-1, an autoantibody (New York esophageal cancer-1). A risk calculating algorithm utilizes machine learning technology to combine the tumor biomarker test values with relevant clinical factors (age, smoking history, and prior lung ailments) to generate a composite score categorizing the risk that the patient has LC. This risk score correlates to the likelihood of having cancer as low, medium, and high.

Percepta Genomic Sequencing Classifier, Veracyte

The Percepta Bronchial Genomic Classifier is a 23-gene, gene expression profiling test that analyzes genomic changes in the airways of current of former smokers to assess an individual's risk of having lung cancer, without the direct testing of a pulmonary nodule. The test is performed with the bronchial brushings collected during bronchoscopy for the diagnosis of suspected lung cancer following indeterminate cytology results. The test aim is to stratify the clinical risk for malignancy and eliminate the need for invasive diagnostic procedures.

Percepta Nasal Swab, Veracyte

The Percepta Nasal Swab test is a nasal genomic classifier that aims assess risk of malignancy in current or former smoking individuals with lung nodules found on CT. The test results are reported as low risk for cancer and continue to monitor with LDCT, moderate risk and to consider non-surgical tissue sampling, or high-risk for cancer and to consider sending patients for surgery and/or

treatment. The Percepta Nasal Swab test was built upon foundational "field of injury" science - through which genomic changes associated with lung cancer can be found in the airways of current and former smokers. Veracyte began making the test available to a limited number of medical centers in October 2021.

SUPPORTIVE LITERATURE

Plasma-Based Proteomic Screening

Silvestri et al (2018) reported the validation of the Xpresys Lung version 2/Nodify XL2 (BDX-XL2) in a prospective multicenter observational study (PulmonAry NOdule Plasma proTeomIc Classifier [PANOPTIC]) that enrolled 685 patients with eight (8) to 30 mm lung nodules. After exclusions, 178 patients remained with a low pretest probability of malignancy ≤50% and were included in the study population. There were 149 benign lung nodules and 29 malignant lung nodules in the study. Of these, 66 were classified as "likely benign", 65 of which had a benign nodule, resulting in 44% of benign lung nodules (65 of 149) being correctly labeled "likely benign," while one (1) of 29 malignant nodules (3%) was misclassified as "likely benign". Of the 71 patients who had invasive procedures, 42 had benign nodules. Use of the integrated proteomic classifier would have reduced the number of patients undergoing an invasive procedure to 27, a 36% relative risk reduction, with one (1) malignant nodule misclassified as benign. Of note, 88 patients were reported to be without follow-up CT scan data at one (1) year and the investigators called for a two (2) year follow up.

Tanner et al (2021) performed an extended analysis and 2-year follow-up of the 392 patients included in the PANOPTIC study. Of the 178 patients with a physician pretest probability of malignancy < 50%, 149 (84%) were benign at year one (1). At year two (2), 17 patients who were categorized as benign previously, were lost to follow up and were excluded reducing the number of patients with benign nodules to 132 at the two (2) year interval and leaving a total of 161 patients (90%) with data available for analysis. All nodules designated as benign at year one (1) remained benign by imaging (e.g., stable or resolved) at year two (2) with no change in pathologic diagnoses or nodule size by CT. Additionally, the area under the curve of the integrated classifier was 0.76 (95% CI, 0.69 to 0.82), which outperformed the physician pretest probability for malignancy (0.69; 95% CI, 0.62 to 0.76) and the Mayo (0.69; 95% CI, 0.62 to 0.76), Veterans Administration (0.6; 95% CI, 0.53 to 0.67), and Brock (0.71; 95% CI, 0.63 to 0.77) models in the lower risk pretest probability (≤50%) cohort.

Tahvilian et al (2023) conducted a prospective correlational study of 151 participants from Mount Sinai Hospital (n = 83) and MD Anderson Cancer Center (n = 68), who were scheduled for a pulmonary biopsy and then enrolled to have a LungLB blood test. Participants enrolled in this study were followed for nine (9) to 24 months following biopsy to confirm malignant or benign diagnosis using standard of care procedures at each site, including CT-based surveillance, repeat biopsy, and/or surgery. Of these 151 participants, 112 participants were diagnosed with malignant lung lesions and 39 participants with benign lung lesions based on blinded nodule biopsy results. LungLB achieved 77% sensitivity and 72% specificity with an AUC of 0.78 for predicting lung cancer in the associated needle biopsy. The clinical trial was limited due to small sample size and COVID-related diagnostic delays. The researchers noted one of the two study sites, MD Anderson Cancer Center, is

in a region with higher incidence of fungal histoplasmosis infections. In this cohort 11 (28.2%) of 39 participants with benign lesions had infectious etiology. Additional studies of the LungLB test are warranted.

Gene Expression Analysis

Vachani et al (2016) reported on rates of invasive procedures from two multicenter trials of patients undergoing bronchoscopy for suspected lung cancer, Airway Epithelium Gene Expression in the Diagnosis of Lung Cancer cohorts (AEGIS I and II). Of 222 patients with low and intermediate pretest probability of cancer, 188 (85%) had an inconclusive bronchoscopy and follow-up procedure data available for analysis. Seventy-seven (41%) patients underwent an additional 99 invasive procedures, which included surgical lung biopsy in 40 (52%) patients. Benign and malignant diseases were diagnosed in 62 (81%) and 15 (19%) patients, respectively. Among those undergoing surgical biopsy, 20 (50%) were performed in patients with benign disease. If the classifier had been used to guide decision-making, procedures could have been avoided in 21 of 42 (50%) of patients undergoing further invasive testing. Among 35 patients with an inconclusive index bronchoscopy who were diagnosed with lung cancer, the sensitivity of the classifier was 89%, with 4 (11%) patients having a false-negative classifier result and may have experienced a delayed diagnosis. The study was limited to 12 months of follow up after the index bronchoscopy. In addition, physicians were blinded to results of the classifier so the impact of the classifier on their decision making was unable to be evaluated. In some patients with a negative classifier result, physicians may still choose to proceed with further invasive testing.

Mazzone et al (2022) conducted a prospective, multicenter, blinded, clinical validation study of 412 patients who were current or former smokers and were undergoing bronchoscopy for suspected lung cancer from the AEGIS I and II trails and the Percepta Registry. The prevalence of malignancy was 39.6% and the ability of the classifier to decrease unnecessary invasive procedures was estimated. Overall, 29% of intermediate-risk lung lesions were down-classified to low-risk with a 91.0% negative predictive value (NPV) and 12.2% of intermediate-risk lesions were up-classified to high-risk with a 65.4% positive predictive value (PPV). In addition, 54.5% of low-risk lesions were down-classified to very- low-risk with >99% NPV and 27.3% of high-risk lesions were up-classified to very high risk with a 91.5% PPV. If the classifier results were used in nodule management, 50% of patients with benign lesions and 29% of patients with malignant lesions undergoing additional invasive procedures could have avoided these procedures. The study was limited to patients with a history of smoking and the follow up period was only 12 months to determine benign status. Additional prospective clinical utility studies would be helpful to further establish the benefits and performance of the classifier in real-world settings.

Flow Cytometry Analysis of Sputum

Lemieux et al (2023) conducted a prospective, multicenter clinical trial of CyPath Lung that evaluated sputum of smokers or former smokers enrolled in a cancer cohort and a non-cancer cohort. Initially 171 sputum samples were analyzed but the study only reports on 150 samples that passed quality control. An analysis pipeline combining automated flow cytometry data processing with machine learning was developed to distinguish cancer from non-cancer samples from 150 patients at high risk of whom 28 had lung cancer. Flow data and patient features were evaluated to identify predictors of

lung cancer. The final model was evaluated on a second, independent group of 32 samples, including six (6) samples from patients diagnosed with lung cancer. Automated analysis combined with machine learning resulted in a predictive model that achieved an area under the ROC curve (AUC) of 0.89 (95% CI 0.83–0.89). The sensitivity and specificity were 82% and 88%, respectively, and the negative and positive predictive values 96% and 61%, respectively. Importantly, the test was 92% sensitive and 87% specific in cases when nodules were<20 mm (AUC of 0.94; 95% CI 0.89–0.99). Testing of the model on an independent second set of samples showed an AUC of 0.85 (95% CI 0.71–0.98) with an 83% sensitivity, 77% specificity, 95% negative predictive value and 45% positive predictive value. This manufacturer's clinical trial is limited by the small, non-diverse sample size and a lack of long term follow up of the non-cancer cohort to confirm they were cancer-free.

Based on the review of the peer reviewed literature, while trial results are promising, further clinical trials are indicated to assess the impact on population health outcomes and clinical decision making. Long-term follow up is needed on these tests to be able to assess their effectiveness in detecting early cancer and risk stratifying indeterminate pulmonary nodules to prevent unnecessary invasive procedures.

PROFESSIONAL GUIDELINE(S)

Currently, professional societies including the American Lung Association, the National Comprehensive Cancer Network (NCCN), and the National Institute for Health and Care Excellence (NICE) do not recommend the use of molecular testing in the management of pulmonary nodules.

U.S. Preventive Service Task Force recommendations (2021) state potential screening modalities that are not recommended because they have not been found to be beneficial include sputum cytology, chest radiography, and measurement of biomarker levels. The paper notes that research is needed to identify biomarkers that can accurately identify persons at high-risk is needed to improve detection and minimize false-positive results.

The American Thoracic Society (ATS) published a position statement on the evaluation of molecular biomarkers for the early detection of lung cancer (Mazzone 2017). They state to support the application of molecular biomarkers in these clinical settings there must be evidence that the molecular biomarker leads to clinical decisions whose benefits outweigh their harms. Although it is tempting to apply novel testing based on promising discovery or validation level studies, the lung cancer community should insist on additional evidence of clinical utility before changing practice. In 2021, ATS published their Core Curriculum adult pulmonary medicine update regarding thoracic oncology which states the use of artificial intelligence with radiomics or integrating artificial intelligence into analysis of genomic, plasma biomarker, biopsy staining pattern, and other patient-derived data are currently under investigation (Garrison 2021). Recent studies have focused on molecular biomarkers to further risk-stratify nodules, but additional clinical utility studies are needed.

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); REVEAL Lung Nodule Characterization (MagArray); 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 these tests.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
0080U (E/I)	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 (BDX-XL2, Biodesix, Inc) [Nodify XL2]
0092U (E/I)	Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy (REVEAL Lung Nodule Characterization, MagArray, Inc)
0317U (E/I)	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm-generated evaluation reported as decreased or increased risk for lung cancer (LungLB, LungLife AI)
0360U (E/I)	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)
0395U (E/I)	Oncology (lung), multi-omics (microbial DNA by shotgun next-generation sequencing and carcinoembryonic antigen and osteopontin by immunoassay), plasma, algorithm reported as malignancy risk for lung nodules in early-stage disease (OncobiotaLUNG, Micronoma)
0406U (E/I)	Oncology (lung), flow cytometry, sputum, 5 markers (meso-tetra [4-carboxyphenyl] porphyrin [TCPP], CD206, CD66b, CD3, CD19), algorithm reported as likelihood of lung cancer (CyPath Lung, Precision Pathology Services)

Code	Description
83520 (*E/I)	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified *E/I when utilized for EarlyCDT lung
81599	Unlisted multianalyte assay with algorithmic analysis
81479 (*E/I)	Unlisted molecular pathology procedure *E/I when utilized for Genesys Biolab's Protein Assays Utilizing Lung Cancer Analytes (PAULAs Test), Veracyte's Percepta Genomic Sequencing Classifier, and Veracyte's Percepta Nasal Swab

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
R91	Abnormal findings on diagnostic imaging of lung
R91.1	Solitary pulmonary nodule
R91.8	Other nonspecific abnormal finding of lung field
Z12.2	Encounter for screening for malignant neoplasm of respiratory organs

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SEARCH TERMS

CyPath Lung, Early CDT Lung, Nodify CDT, Nodify XL2, Xpresys Lung, Xpresys Lung 2, BDX-XL2, OncobiotaLUNG, ReVeal Lung Nodule Characterization, Protein Assays Utilizing Lung Cancer Analytes (PAULAs Test), Percepta Genomic Sequencing Classifier, Percepta Nasal Swab

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Based upon review, molecular testing for the management of pulmonary nodules is not addressed in a National or Regional Medicare coverage determinations or policies.

Please refer to the Medicare Managed Care Manual [accessed 2025 Sep 9] Available from: 100-16 | CMS Medicare Managed Care Manual

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION

Committee Approval Dates

10/19/23, 10/17/24, 10/16/25

Date	Summary of Changes
10/16/25	Annual review, policy intent unchanged.
01/01/25	Summary of changes tracking implemented.
02/15/24	Original effective date