

Medical Policy



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***Current Policy Effective Date: 11/1/26**
(See policy history boxes for previous effective dates)

Title: Molecular Testing in the Management of Pulmonary Nodules

Description

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.

Medical Policy Statement

Plasma-based proteomic screening, including but not limited to Nodify XL2® (BDX-XL2) and Nodify CDT® in individuals with undiagnosed pulmonary nodules detected by computed tomography is considered **experimental/investigational**. There is insufficient evidence to determine that the technology results in an improvement in net health outcomes.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81479

0080U

0360U

Notes:

- Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.
- Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

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 measures autoantibodies associated with tumor-associated 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 used in the management of pulmonary nodules to help rule out or rule in the need for 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 with 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 gene expression profiling. An important role of gene expression profiling in molecular diagnostics is to detect cancer-associated gene expression in clinical samples to assess the risk for malignancy.

Summary of Evidence

For individuals with undiagnosed pulmonary nodules detected by computed tomography who receive plasma-based proteomic screening, the evidence includes prospective cohorts, retrospective studies, 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 (Xpresys Lung, and Xpresys Lung version 2 [now Nodify XL2]) of a proteomic classifier. The Nodify XL2 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 the 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 ($\leq 50\%$) 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. Complete validation results are not available for Nodify CDT, and no clinical validation studies were

identified the Nodify Lung testing strategy. Validation in an independent sample in the intended use population with additional probability models is needed. Indirect evidence suggests that a proteomic classifier with a high negative predictive value has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. However, long-term follow-up data would be required to determine the survival outcomes in patients with a missed diagnosis of lung cancer at earlier, more treatable stages. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

PLASMA-BASED PROTEOMIC SCREENING OF PULMONARY NODULES

Clinical Context and Test Purpose

The purpose of plasma-based proteomic screening in individuals with undiagnosed pulmonary nodule(s) is to stratify clinical risk for malignancy and eliminate or necessitate the need for invasive diagnostic procedures.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Nodify XL2 (BDX-XL2; previously Xpresys Lung and Xpresys Lung 2)

Several studies were identified that reported on the development and validation of Xpresys Lung, and Xpresys Lung 2/Nodify XL2 (BDX-XL2).

Li et al (2013) reported on an initial development that was based on a 13-protein plasma classifier.²

Vachani et al (2015) reported on the validation of Xpresys Lung, which was an 11-protein plasma classifier designed to identify likely benign lung nodules (Tables 1 and 2).³

This retrospective, blinded analysis evaluated existing samples (N=141) associated with indeterminate pulmonary nodules 8 to 30 mm in diameter. The performance of the classifier in identifying benign nodules was tested at predefined reference values. For example, using a population-based non-small-cell lung cancer prevalence estimate of 23% for indeterminate pulmonary nodules 8 to 30 mm in diameter, the classifier identified likely benign lung nodules with a 90% negative predictive value (NPV) and a 26% positive predictive value, at 92%

sensitivity and 20% specificity, with the lower bound of the classifier's performance at 70% sensitivity and 48% specificity. Additional sample diagnostic characteristics, selected to keep the study's target negative predictive value of 90%, are shown in Table 2. Classifier scores for the overall cohort were statistically independent of patient age, tobacco use, nodule size, and chronic obstructive pulmonary disease diagnosis. The classifier also demonstrated incremental diagnostic performance in combination with a 4-parameter clinical model.

Vachani et al (2015) reported on a multicenter prospective-retrospective study of patients with indeterminate pulmonary nodules.⁴ A plasma protein classifier was used on 475 patients with nodules 8 to 30 mm in diameter who had an invasive procedure to confirm the diagnosis. Using the classifier, 32.0% (95% confidence interval [CI], 19.5 to 46.7) of surgeries and 31.8% (95% CI, 20.9 to 44.4) of invasive procedures (biopsy and/or surgery) on benign nodules could have been avoided, while 24.0% (95% CI, 19.2 to 29.4) of patients with malignancy would have been triaged to CT surveillance. By comparison, 24.5% (95% CI, 16.2 to 34.4) of patients with malignancy were routed to CT surveillance using clinical parameters alone.

Kearney et al (2017) conducted an exploratory study that combined the 11-protein plasma classifier (Xpresys Lung) with clinical risk factors using 222 samples associated with a lung nodule of 8 to 20 mm in diameter from the reclassification study by Vachani et al (2015) described above.⁵ The study determined that the ratio of LG3BP to a normalizer protein C163A was the diagnostic and normalizer protein pair with the highest area under the curve (60%). At a sensitivity of 90% and specificity of 33%, the ratio of the proteomic marker was more accurate than clinical risk factors, and the combination of the clinical risk factors with the proteomic markers was more accurate than either alone. This study led to the development of the Xpresys Lung version 2 (Nodify XL2), which includes LG3BP, C163A, and clinical risk factors.

Silvestri et al (2018) reported the validation of the Xpresys Lung version 2 (Nodify XL2) in a prospective multicenter observational study (Pulmonary Nodule Plasma Proteomic Classifier [PANOPTIC]) that enrolled 685 patients with lung nodules of 8 to 30 mm and a low pretest probability of malignancy $\leq 50\%$.⁶ After exclusions for missing clinical data or a pretest probability of $> 50\%$, 178 patients remained in the intended use population. Of these, 66 were classified as likely benign, 65 of which had a benign nodule, while 1 of 29 malignant nodules (3%) was misclassified as likely benign. Of the 149 benign nodules in the study, 44% were correctly classified 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 1 malignant nodule misclassified as benign.

In an extended analysis and 2-year follow-up of the PANOPTIC trial, Tanner et al (2021) found that all nodules designated as benign at year 1 remained benign by imaging at year 2 with no change in pathologic diagnoses or nodule size by CT.⁷ 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 ($\leq 50\%$) cohort.

Long et al (2025) published an analysis of banked samples from 2 prospective cohort studies (PANOPTIC and the unpublished Fred Hutchinson Cancer Center cohort).⁸ PANOPTIC used

the Nodify XL2 test and the Fred Hutchinson Cancer Center cohort used the Nodify CDT test. Samples from 447 patients were evaluated. The cancer prevalence was 55%. Autoantibody levels were moderate in 6.7% of the total cohort and high in 6.9% of the total cohort. In the combined cohort, the sensitivity, specificity, positive predictive value, and false positive rate were 16%, 90%, 66%, and 10%, respectively. Use of the test allowed for reclassification of 16 intermediate nodules to high risk, compared to reclassification of 10 benign nodules. Among 222 patients who received both a Nodify test and positron emission tomography, sensitivity was lower with the Nodify test (17% vs. 75%, respectively; $p < .001$) and specificity was higher with the Nodify test (93% vs. 58%; $p < .001$). False positive tests occurred in 7% of patients who received the Nodify test versus 42% with positron emission tomography. Interpretation of these results is limited by the combined analysis of patients who received 2 different tests.

Pitcher et al (2026) reported the pooled results of 4 cohort studies that used a Nodify test, including Silvestri et al (2018), Long et al (2025), Pritchett et al (2023; summarized in the clinical utility section below), and the ongoing CLARIFY study (NCT06728319).⁹ A total of 1164 patients with lung nodules between 4 and 30 mm were included in the analysis. The cancer prevalence was 35%, with 5.8% having a moderate autoantibody result and 5.6% having a high autoantibody result. At the moderate level threshold, sensitivity, specificity, and positive predictive value were 16%, 91%, and 50%, respectively. At the high level threshold, sensitivity, specificity, and positive predictive value were 9%, 96%, and 57%, respectively. Use of the test allowed for reclassification of 10% of intermediate-risk cancers to high risk, compared to reclassification of 3% of benign nodules. A limitation of these results is the combined analysis of patients who received different Nodify tests.

Table 1. Study Characteristics of Clinical Validity

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
Vachani et al (2015) ³	141 samples associated with indeterminate pulmonary nodules	Retrospective analysis with existing samples		Selected to keep NPV of 90%		Yes	Xpresys Lung
Silvestri et al (2018) ⁶ ; PANOPTIC	178 patients with 8 to 30mm lung nodules and low pretest probability	Prospective multicenter observational	Definitive diagnosis, nodule resolution, or 1 year of radiographic stability	NR	Retrospective evaluation of performance	Yes	Xpresys Lung version 2

NPV: negative predictive value; NR: not reported

Table 2. Summary of Diagnostic Performance Studies for Proteomic Tests to Predict Malignancy

Study	Prevalence, %	Reference Value	Sensitivity, % (95% CI)	Specificity, %	NPV, %	PPV, %
Vachani et al (2015) ^{10,3}	23.1	0.47	69.5 (NR)	48.0 (NR)	84.0	28.6
	23.1	0.39	83.8 (NR)	32.3 (NR)	86.9	27.1

	23.1	0.36	82.1 (NR)	20.4 (NR)	89.6	25.8
Silvestri et al (2018) ⁶ PANOPTIC	16.3	NR	97 (82 to 100)	44 (36 to 52)	98 (92 to 100)	NR

CI: confidence interval; NPV: negative predictive value; NR: not reported; PANOPTIC: Pulmonary Nodule Plasma Proteomic Classifier; PPV: positive predictive value

Limitations of the two validation studies are described in Tables 3 and 4. The primary limitation of the study by Vachani et al (2015) is that the technology is very different from the current marketed version. The primary limitation of the study by Silvestri et al (2018) 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.

Table 3. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Vachani et al (2015) ³		3. Not the current version of the test.			
Silvestri et al (2018) ⁶ PANOPTIC	4. The enrolled patients included those who were outside of intended use.				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 4. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Vachani et al (2015) ³						
Silvestri et al (2018) ⁶ PANOPTIC				2. Data were collected but not reported for the 214 patients with pretest probability >50%	2. A high number of patients (n=234) were excluded	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

b Blinding key: 1. Not blinded to results of reference or other comparator tests.

c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Nodify CDT

The Long et al (2025) study discussed above presented some results of the unpublished Fred Hutchinson Cancer Center cohort study.⁸ The cancer prevalence in this cohort was 56%. Autoantibody levels were moderate in 10% of patients and high in 4.3% of patients. Sensitivity, specificity, positive predictive value, and false positive rate were 15%, 85%, 56%, and 15%, respectively.

Nodify Lung

No recent literature meeting the evidence requirements of this review was identified for Nodify Lung (performing the Nodify XL2 and Nodify CDT tests in conjunction) that meets the evidence requirements of this review.

Section Summary: Clinically Valid

Clinical validation studies were identified for 2 versions (Xpresys Lung, and Xpresys Lung 2 [now Nodify XL2]) of a proteomic classifier. The Nodify XL2 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 the version 2 (Xpresys Lung 2 [now Nodify XL2]) 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 a low to moderate pretest probability ($\leq 50\%$) 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. Only partial validation results for the Nodify CDT study have been published. No relevant recent studies were identified for Nodify Lung. Limitations included a small sample size and use in conjunction with only 1 type of testing model. Validation in an independent sample in the intended use population with additional probability models is needed.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No evidence directly demonstrating improved outcomes in patients managed with the Xpresys Lung Xpresys Lung 2/Nodify XL2 (BDX-XL2), or Nodify CDT tests, or the Nodify Lung testing strategy was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence was developed, which addresses 2 key questions: (1) Does the use of a proteomic classifier with a high negative predictive value (NPV) in patients with undiagnosed pulmonary nodules detected by CT change clinical management (in this case, reduction of invasive procedures) and (2) Do those management changes improve outcomes relative to a clinical classifier?

Changes in Management

The patient population for which a proteomic classifier with a high NPV is used is individuals with undiagnosed pulmonary nodules detected by CT.

Indirect evidence regarding Xpresys Lung version 2 suggests that 36% of invasive procedures (biopsy and/or surgery) on benign nodules could have been avoided, if the test is used in patients with a low to moderate ($\leq 50\%$) pretest probability of malignancy. Three percent of malignant lesions may be missed, although these patients would be followed by CT to verify lack of progression.

One decision impact study reporting on clinical management changes, but not on outcomes after decisions for invasive procedures were made, has suggested that, in at least some cases, decisions for invasive procedures may be changed. Pritchett et al (2023) reported on the impact of the Nodify XL2 test on physician decision-making for recommending invasive procedures among patients with undiagnosed pulmonary nodules detected by CT in the observation of residual cancer with liquid biopsy evaluation ORACLE study.¹¹ This propensity score matching cohort study compared patients with a low to moderate ($\leq 50\%$) pretest probability of malignancy in the ORACLE prospective, multicenter, observational registry (classifier arm) to retrospective chart review of control patients treated with typical care. The results revealed that classifier testing result might reduce invasive procedure recommendations in patients diagnosed with benign disease. Of the 197 patients tested in the classifier group, 162 (82%) were benign and 35 (18%) were malignant. Patients with a benign nodule in the classifier arm were 74% less likely to undergo an invasive procedure as compared to patients in the control group (absolute difference, -14%; 95% CI, -19.5% to -7.9%; $p < .001$). There was 1 invasive procedure per 20 patients in the benign nodule classifier group compared to 1 invasive procedure per 5 patients in the control group (odds ratio, 0.23; 95% CI, 0.09 to 0.53; $p < .001$). In other words, for every 7 benign nodules tested with the Nodify XL2 test, 1 unnecessary invasive procedure was avoided. The rate of patients in the classifier group with a malignant nodule was not statistically different than the control group.

Improved Outcomes

Indirect evidence suggests that use of a proteomic classifier with a high NPV has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. Compared to the standard care plan, some patients without cancer will have avoided an unnecessary invasive procedure, which is weighed against the increase in missed cancers in patients who had lung cancer but tested as negative on the proteomic classifier with high NPV test.

Whether the tradeoff between avoiding unneeded surgeries and the potential for missed cancer is worthwhile depends, in part, on patient and physician preferences. Missed malignancies would likely continue to be followed by active surveillance by low dose CT

imaging. In the context of lung cancers, overall survival depends on detection of lung cancer at early, more treatable stages.

Avoiding invasive procedures in situations where patients are at very low likelihood of having lung cancer is likely beneficial, given the known complications (e.g., pneumothorax). However, reductions in unnecessary invasive procedures must be weighed against outcomes and harms associated with a missed diagnosis of lung cancer at earlier, more treatable stages.

Section Summary: Clinically Useful

Indirect evidence suggests that a proteomic classifier with a high NPV has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. However, stronger clinical validity data would be needed to rely on indirect evidence for clinical utility, or long-term follow-up data would be required to determine the survival outcomes in patients with a missed diagnosis of lung cancer at earlier, more treatable stages.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.¹²

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.¹³ 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."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for non-small cell lung cancer, small cell lung cancer, or lung cancer screening do not mention plasma-based

proteomic screening testing or gene expression profiling as a potential diagnostic or screening tool.^{14,15,16}

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently ongoing trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT06728319 ^a	A Multicenter, Retrospective, Chart Review Study Evaluating the Impact and Utility of the Blood-Based Proteomic Integrated Classifier and Auto-Antibody Tests in the Real-World (CLARIFY)	4000	July 2027
NCT06426628 ^a	Clinical Utility of Management of Patients With CT and LDCT Identified Pulmonary Nodules Using the Percepta Nasal Swab Classifier (NIGHTINGALE)	2400	Mar 2027
NCT04171492 ^a	A Multicenter, Randomized Controlled Trial, Prospectively Evaluating the Clinical Utility of the Nodify XL2 Proteomic Classifier in Incidentally Discovered Low to Moderate Risk Lung Nodules	2000	Dec 2026

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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); and Nodify CDT (Biodesix); are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

The Percepta Genomic Sequencing Classifier (Veracyte) is no longer a marketed product, however, Veracyte is developing a nasal swab test that leverages the same RNA-based "field of injury" genomic analysis of bronchial epithelial cells to risk-stratify patients with non-diagnostic results for suspicious lung nodules. Veracyte's lung cancer strategy now centers on the Percepta Nasal Swab test, currently designated as "in pipeline" on the company's website. This test applies the same foundational field-of-injury science but shifts the collection site from the bronchial airway to the nasal epithelium, enabling a simple, non-invasive, office-based sample collection without the need for bronchoscopy.

Government Regulations

National:

Medicare National Coverage

Some plans will provide limited coverage for the BDX-XL2 test (Biodesix) for the management of a lung nodule between 8 and 30 mm 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. Per Biodesix, both the Nodify XL2 and Nodify CDT tests are \$0 out of pocket for covered Medicare beneficiaries.¹⁷

Local:

Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD): BDX-XL2 (L37216)
Original Effective Date: 09/16/2017
Revision Effective Date: 03/30/2023

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding: BDX-XL2 (A57558)
Original Effective Date: 11/28/2019
Revision Effective Date: 03/30/2023

Group 1 codes: 0080U

Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD): MoIDX: Percepta® Bronchial Genomic Classifier (L37195)
Original Effective Date: 09/16/2017
Revision Effective Date: 10/26/2023
Retirement Date: 9/22/2024

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding: MoIDX: Percepta® Bronchial Genomic Classifier (A57584)
Original Effective Date: 10/26/2023
Retirement Date: 09/22/2024

Group 1 codes: 81479

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicaid Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through June, 2026, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/18	7/9/18	6/29/18	Joint policy established
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance; reference 7 added. Title change from: "Molecular Testing (Proteomic and Gene Expression) in the Management of Pulmonary Nodules" to "Molecular Testing in the Management of Pulmonary Nodules".
9/1/21	6/15/21		Routine maintenance
11/1/21	8/17/21		Routine maintenance. Ref 7 added.
11/1/22	8/16/22		Routine maintenance Ref 14 added (ls)
11/1/23	8/15/23		Routine maintenance (jf) Vendor Managed: NA Ref added: 12,13,18,19,20
11/1/24	8/20/24		Routine maintenance (jf) Vendor Managed: NA Ref added: 9,10 -Edited Medical Policy Statement: Added Nodify CDT®, and REVEAL Lung Nodule Characterization (MagArray) as E/I. - Added 0360U as E/I to policy that represents Nodify CDT - Added 0092U as E/I to policy to include REVEAL Lung Nodule Characterization, MagArray, Inc. • Edit to MPS The peer reviewed literature has not demonstrated improved clinical outcomes
11/1/25	8/19/25		Routine maintenance (jf) Vendor Managed: NA Added Description and background separated Description added and background separated, movement of policy

			language and formatting to assist with flow Edited MPS with updated language “There is insufficient evidence to determine that the technology results in an improvement in net health outcomes”.
11/1/26	8/18/26		Routine maintenance (jf/fr) Vendor Managed: NA Minor Edits: • MPS edited- The policy statement for the Percepta Genomic Sequencing Classifier was removed as the product is no longer marketed. The REVEAL Lung Nodule Characterization by MagArray was removed from the policy statements as the company is no longer in business. Evidence review for the Percepta Genomic Sequencing Classifier was removed. • Update to regulatory section: Percepta Genomic Sequencing Classifier (Veracyte) is no longer a marketed product. However, Veracyte is developing a nasal swab test that leverages the same RNA based "field of injury" genomic analysis of bronchial epithelial cells to risk-stratify patients with non-diagnostic results for suspicious lung nodules. • Delete 0092U from policy • Formatting changes made: ○ Notes edited in code section ○ Administrative Guidelines removed from Blue Care Network Coverage page

Next Review Date: 3rd Qtr, 2027

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: MOLECULAR TESTING IN THE MANAGEMENT OF PULMONARY NODULES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.