Medical Policy

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Title: Molecular Testing in the Management of Pulmonary Nodules

Description/Background

PULMONARY NODULES

Pulmonary nodules are a common clinical problem that may be found incidentally on a chest x-ray or computed tomography (CT) scan or during lung cancer screening studies of smokers. The primary question after the detection of a pulmonary nodule is the probability of malignancy, with subsequent management of the nodule based on various factors such as the radiographic characteristics of the nodules (eg, size, shape, density) and patient factors (eg, age, smoking history, previous cancer history, family history, environmental/occupational exposures). The key challenge in the diagnostic workup for pulmonary nodules is appropriately ruling in patients for invasive diagnostic procedures and ruling out patients who should forgo invasive diagnostic procedures. However, due to the low positive predictive value of pulmonary nodules detected radiographically, many unnecessary invasive diagnostic procedures and/or surgeries are performed to confirm or eliminate the diagnosis of lung cancer.

PROTEOMICS

Proteomics is the study of the structure and function of proteins. The study of the concentration, structure and other characteristics of proteins in various bodily tissues, fluids, and other materials has been proposed as a method to identify and manage various diseases, including cancer. In proteomics, multiple test methods are used to study proteins. Immunoassays use antibodies to detect the concentration and/or structure of proteins. Mass spectrometry is an analytic technique that ionizes proteins into smaller fragments and determines mass and composition to identify and characterize them.

Plasma-Based Proteomic Screening for Pulmonary Nodules
Plasma-based proteomic screening has been investigated to risk-stratify pulmonary nodules as likely benign to increase the number of patients who undergo serial CT scans of their nodules (active surveillance), instead of invasive procedures such as CT-guided biopsy or surgery. Additionally, proteomic testing may also determine a likely malignancy in clinically low-risk or intermediate-risk pulmonary nodules, thereby permitting earlier detection in a subset of patients.

Nodify XL2 (BDX-XL2) is a 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.

REVEAL Lung Nodule Characterization (MagArray) is a plasma-protein biomarker test that may aid clinicians in characterizing indeterminate pulmonary nodules (4 to 30 mm) in current smokers 25 years of age and older. The test is based on a multianalyte assay with a proprietary algorithmic analysis using immunoassay, microarray, and magnetic nanoparticle detection techniques to obtain laboratory data for calculation of the risk score for lung cancer. The REVEAL Lung Nodule Characterization is presented on a scale from 0 to 100 with a single cut point at 50. The score is based on the measurement of 3 clinical factors (age, sex, and nodule diameter) and 3 proteins (epidermal growth factor receptor, prosurfactant protein B, and tissue inhibitor of metalloproteinases 1) associated with the presence of lung cancer. It may aid a clinician in the decision to perform a biopsy or to consider routine monitoring. It is not intended as a screening or stand-alone diagnostic assay.

GENE EXPRESSION PROFILING
Gene expression profiling (GEP) is the measurement of the activity of genes with cells. Messenger RNA serves at 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.

Gene Expression Profiling for an Indeterminate Bronchoscopy Result

The first generation Percepta® Bronchial Genomic Classifier was a 23-gene gene expression profiling test that analyzed genomic changes in the airways of current or former smokers to assess a patient's risk of having lung cancer, without 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 subsequent management of pulmonary nodules (eg, active surveillance or invasive diagnostic procedures), and does not diagnose lung cancer.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Xpresys Lung 2, 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 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.

Medical Policy Statement

- Plasma-based proteomic screening, including but not limited to Nodify XL2® (BDX-XL2), Nodify CDT®, and REVEAL Lung Nodule Characterization (MagArray),in patients with undiagnosed pulmonary nodules detected by computed tomography is considered **experimental/investigational**. The peer reviewed literature has not demonstrated improved clinical outcomes

- Gene expression profiling on bronchial brushings, including but not limited to the Percepta® Genomic Sequencing Classifier, in patients with indeterminate bronchoscopy results from undiagnosed pulmonary nodules is considered **experimental/investigational**. The peer reviewed literature has not demonstrated improved clinical outcomes

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

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

81479 0080U 0092U 0360U

Note: 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.

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of this review, and credible information on technical reliability is available from other sources.

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.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with undiagnosed pulmonary nodules detected by computed tomography (CT) . In particular, as outlined in the evidence-based American College of Chest Physicians guidelines (2013) on the diagnosis and management of lung cancer, decision-making about a single indeterminate lung nodule 8 to 30 mm in diameter on a CT scan is complicated, requiring input about the patient's pretest probability of lung cancer, the characteristics of the lung nodule on CT, and shared decision-making between the patient

and physician about follow up.[1] Therefore, additional information in the segment of individuals with an indeterminate lung nodule 8 to 30 mm in diameter would be particularly useful.

Interventions

The test being considered is plasma-based proteomic screening. Of particular focus are the Nodify XL2 (BDX-XL2; formerly Xpresys Lung 2) Nodify CDT and REVEAL Lung Nodule Characterization tests. Nodify XL2 BDX-XL2 measures the abundance of 2 plasma proteins (LG3BP and C163A) and combines the results with 5 clinical risk factors (age, smoking status, nodule diameter, edge characteristics, and location) to provide a posttest probability of a lung nodule being benign. Nodify CDT measures 7 autoantibodies associated with tumor antigens to provide a post-test probability of a lung nodule being malignant. These 2 tests are offered alone, or in conjunction with each other as the Nodify Lung. REVEAL Lung Nodule Characterization (MagArray) measures 3 plasma proteins (epidermal growth factor receptor, prosurfactant protein B, and tissue inhibitor of metalloproteinases 1) associated with the presence of lung cancer and combines the results with 3 clinical factors (age, sex, and nodule diameter) to provide algorithmic scoring to quantify the likelihood of lung cancer as a risk assessment tool.

Comparators

The following practice is currently being used: standard diagnostic workup using clinical and radiographic risk factors.

Outcomes

The potential beneficial outcomes of primary interest are avoiding an unneeded invasive biopsy of a nodule that would be negative for lung cancer or initiating a biopsy for a nodule that would otherwise have been followed with serial CTs.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary invasive diagnostic procedures and procedure-related complications. False-negative test results can lead to lack of pulmonary nodule surveillance or lack of appropriate invasive diagnostic procedures to diagnose a malignancy.

The time frame for evaluating test performance varies the initial CT scan to an invasive diagnostic procedure to up to 2 years, which would be the typical follow-up needed for some lung nodules.

Study Selection Criteria

For the evaluation of clinical validity of the plasma-based proteomic screening test, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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 ≤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 (≤50%) cohort.

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)[8,3]	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 and Nodify Lung

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

REVEAL Lung Nodule Characterization

Trivedi et al (2018) reported on a clinical validation study for the REVEAL Lung Nodule Characterization test using retrospective human plasma samples and associated clinical data from current smokers aged 25 to 85 years of age with indeterminate lung nodules measuring 4 to 30 mm in diameter.[9.] Plasma samples from patients with metastatic disease or previously diagnosed lung cancer were excluded. The REVEAL test was used in conjunction with the Veteran's Affairs (VA) Clinical Factors Model, with the objective to add discriminatory information when the VA model classified samples as inconclusive or intermediate risk. Ninety-seven samples were included in the validation study. Of the 97 samples, 68 were grouped as having intermediate risk by the VA model. The REVEAL model correctly identified 44 (65%) of these intermediate-risk samples as low (n=16) or high (n=28) risk. The REVEAL assay NPV was 94% and its sensitivity was 94%, suggesting potential application as a rule-out test to increase the confidence of providers to avoid aggressive interventions for patients for whom the VA model result is inconclusive or intermediate risk.

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 and another lung nodule characterization test (REVEAL). 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 (≤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 relevant recent studies were identified for Nodify CDT or Nodify Lung. The REVEAL validation study was a retrospective study that demonstrated use as a rule-out test in conjunction with the VA Clinical Factors Model when the samples were considered inconclusive or intermediate risk by the VA model. The REVEAL model subsequently correctly identified 65% intermediate-risk samples as either low or high risk. The NPV and sensitivity were both 94%. Limitations included a small sample size and use in conjunction with just 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 (≤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 ORACLE study.[10.] This propensity score matching cohort study compared patients with a low to moderate (≤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 (eg, 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.

GENE EXPRESSION PROFILING OF INDETERMINATE BROCHOSCOPY RESULTS

Clinical Context and Test Purpose
The purpose of gene expression profiling (GEP) on bronchial brushings in individuals who undergo bronchoscopy for the diagnosis of suspected lung cancer but who have an indeterminate cytology result is to stratify the clinical risk for malignancy and eliminate the need for invasive diagnostic procedures.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with undiagnosed pulmonary nodules following indeterminate bronchoscopy results for suspected lung cancer.

Interventions
The relevant intervention of interest is GEP of bronchial brushings:Percepta Genomic Sequencing Classifier (GSC), previously Percepta Bronchial Genomic Classifier (BGC)..

Comparators

The following practice is currently being used: standard diagnostic workup. The management of patients with suspected lung cancer who have an indeterminate bronchoscopy result is not entirely standardized. However, it is likely that in standard practice many patients would have a surgical biopsy, transthoracic needle aspiration, or another test, depending on the location of the nodule. In 2013, the American College of Chest Physicians recommended bronchoscopy to confirm diagnosis in patients who have suspected lung cancer with a central lesion.[11] If bronchoscopy results are non-diagnostic and suspicion of lung cancer remains, additional testing is recommended (grade 1B recommendation).

Outcomes

The potential beneficial outcomes of primary interest is avoiding an unneeded invasive biopsy of a nodule hat would be negative for lung cancer.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary invasive diagnostic procedures and procedure-related complications. False-negative test results can lead to lack of pulmonary nodule surveillance or lack of appropriate invasive diagnostic procedures to diagnose malignancy.

The time frame for outcome measures varies from the short-term development of invasive diagnostic procedure-related complications to long-term procedure-related complications, development of malignancy, or overall survival.

Study Selection Criteria

Selection criteria for studies to assess whether a test is clinically valid are described in the first indication.

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

Whitney et al (2015) reported on the development and initial validation of an RNA-based gene expression classifier from airway epithelial cells designed to be predictive of cancer in current and former smokers undergoing bronchoscopy for suspected lung cancer.[12] Samples were from patients in the Airway Epithelium Gene Expression In the DiagnosiS of Lung Cancer (AEGIS) trials, which were 2 prospective, observational, cohort studies (AEGIS-1, AEGIS-2), for current or former smokers undergoing bronchoscopy for suspected lung cancer. Cohort details are described in Silvestri et al (2015), below. A total of 299 samples from AEGIS-1 (223 cancer-positive and 76 cancer-free subjects) were used to derive the classifier. Data from 123 patients in a prior study with a nondiagnostic bronchoscopy were used as an independent test set. In the final model, the classifier included 17 genes, patient age, and gene expression correlates, and was reported as a dichotomous score (≥0.65 as cancer positive and <0.65 as cancer negative). The performance characteristics of the classifier in the training and test set are shown in Table 6.

Silvestri et al (2015) reported on the diagnostic performance of the gene expression classifier developed in Whitney et al (2015), in a sample of 639 patients enrolled in 2 multicenter prospective studies (AEGIS-1, N=298 patients; AEGIS-2, N=341 patients).[13] Study characteristics are summarized in Table 5. The study enrolled patients who were undergoing clinically indicated bronchoscopy for a diagnosis of possible lung cancer and had a history of smoking. Before the bronchoscopy, the treating physician assessed each patient's probability of having cancer with a 5-level scale (<10%, 10% to39%, 40 to60%, 61%85%, and >85%). Patients were followed until a diagnosis was established (either at the time of bronchoscopy or subsequently by another biopsy means) or until 12 months after bronchoscopy.

A total of 855 patients in AEGIS-1 and 502 patients in AEGIS-2 met enrollment criteria.[13] After exclusions due to sample quality issues, loss to follow up, lack of final diagnosis, or non-primary lung cancer, 341 subjects were available in the validation set for AEGIS-2. For AEGIS-1, patients were randomized to the development (described above) or validation (n=298) sets. Of the 639 patients in the validation study who underwent bronchoscopy, 272 (43%; 95% CI 39 to 46) had a nondiagnostic examination. The prevalence of lung cancer was 74% and 78% in AEGIS-1 and AEGIS-2, respectively. The overall test characteristics in AEGIS-1 and AEGIS-2 are summarized in Table 6. The classifier improved the prediction of cancer compared with bronchoscopy alone, but comparisons with a clinical predictor were not reported. For the subset of 272 patients with a nondiagnostic bronchoscopy, the classifier performance was presented by the pretest physician-predicted risk of cancer. For most subpopulations, there was a very high NPV. However, there were 13 false negatives, 10 of which were considered at high risk (>60%) of cancer pre-bronchoscopy. Study limitations are summarized in Tables 7 and 8.

Vachani et al (2016) reported on rates of invasive procedures from AEGIS-1 and -2.[14] Of 222 patients, 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 ultimately 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 (50%) of 42 patients who had additional invasive testing. Further, 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. Invasive procedures after an inconclusive bronchoscopy occur frequently, and most are performed in patients ultimately diagnosed with benign disease.

Mazzone et al (2022) conducted a prospective, multicenter, blinded, clinical validation study on individuals (N=412) who currently or formerly smoked undergoing bronchoscopy for suspected lung cancer from the AEGIS-1/AEGIS-2 cohorts and the Percepta Registry. [15]The sensitivity, specificity, and predictive values were calculated using predefined thresholds. Study characteristics and results are summarized in Tables 5 and 6, respectively. Investigators noted that Percepta GSC performance was similar between the AEGIS-1 and -2 cohorts and the Percepta Registry with an overall area under the curve of 0.73 (95% CI, 68.3 to 78.4), demonstrating the robustness of the classifier performance across different patient cohorts. Investigators also estimated the potential utility of Percepta GSC in decreasing invasive procedure utilization, had the classifier result been available to manage these lesions.

It was determined that, 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. Study limitations are summarized in Table 7.

Table 5. 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	Comments
Silvestri et al (2015)[13]	639 Current or former smokers undergoing bronchoscopy for suspected lung cancer (White, 76% to 78%; Black, 18% to 19%; Other, 1% to 5%)	Prospective, observational, cohort studies	Diagnosis or until 12 months after bronchoscopy	NR	Following diagnosis or 12 months	Yes	Percepta GSA 272 patients had a nondiagnostic bronchoscopy and were included in the analysis
Mazzone et al (2022)[15]	412 current or former smokers undergoing bronchoscopy for suspected lung cancer	Prospective, multicenter study	Diagnosis or until 12 months after bronchoscopy	NR	Following diagnosis or 12 months	Yes	Percepta GSA

BGC: bronchial genomic classifier; GSC: genomic sequencing classifier;
NR: not reported

Table 6. Summary of Clinical Validity Studies for Gene Expression Classifier to Predict Malignancy in Bronchial Samples

Study	Population	AUC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Percepta GSC Result	Post-test NPV or PPV, % (95% CI)	% Reclassified Risk of Malignancy
Whitney et al (2015) [12]	Training set, entire population (n=299)	0.78 (0.73 to 0.82)	93	57					
	Training set, subset with nondiagnostic bronchoscopy (n=134)	0.78 (0.71 to 0.85)							
	Test set with nondiagnostic bronchoscopy (n=123)	0.81 (0.73 to 0.88)	92 (78 to 98)	53 (42 to 63)	47 (36 to 58)	94 (83 to 99)			
Silvestri et al (2015) [13]	AEGIS-1 (n=298)	0.78 (0.73 to 0.83)	88 (83 to 95)	47 (37 to 58)					

	AEGIS-2 (n=341)	0.74 (0.68 to 0.80)	89 (84 to 92)	47 (36 to 59)					
	Subset of all patients with nondiagnostic bronchoscopy, by pretest cancer probability risk								
	Risk <10% (n=61)				7 (1 to 24)	100 (89 to 100)			
	Risk 10%-60% (n=84)				40 (27 to 55)	91 (75 to 98)			
	Risk >60% (n=108)				84 (75 to 81)	38 (15 to 65)			
	Risk unknown (n=19)				47 (21 to 73)	100 (40 to 100)			
Mazzone et al (2022) [15]	Low pre-test risk of malignancy (n=80 [4 malignant, 68 benign, 8 clinical benign]); cancer prevalence 5.0%		57.4 (44.8 to 69.3)[a]	100 (39.8 to 100)[b]			Very low	NPV: 100 (91.0 to 100)	54.5
	Intermediate pre-test risk of malignancy (n=188 [53 malignant, 102 benign, 33 clinical benign]); cancer prevalence 28.2%		37.3 (27.9 to 47.4)[a]	90.6 (79.3 to 96.9)[b]			Low	NPV: 91.0 (80.8 to 96.0)	29.4
			94.1 (87.6 to 97.8)[a]	28.3 (16.8 to 42.3)[b]			High	PPV: 65.4 (43.8 to 82.1)	12.2
	High pre-test risk of malignancy (n=144 [106 malignant, 34 benign, 4 clinical benign]); cancer prevalence 73.6%		91.2 (76.3 to 98.1)[a]	34.0 (25.0 to 43.8)[b]			Very high	PPV: 91.5 (77.9 to 97.0)	27.3

AUC: area under the curve; CI: confidence interval; GSC: genomic sequencing classifier; NPV: negative predictive value; PPV: positive predictive value.
[a] Sensitivity is calculated on malignant patients only.
[b] Specificity is calculated on benign patients only, excluding clinical benign.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Silvestri et al (2015)[13]	4. Only included patients with a history of smoking				
Mazzone et al (2022)[15]	4. Only included patients with a history of smoking				1. Follow-up only required to be 12 months to determine benign status, thus a few indolent lung cancers could have been present

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 8. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Silvestri et al (2015)[13]					2. High number of excluded samples	

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.Timingof 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.Expertiseof 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.Highnumber 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.

Section Summary: Clinically Valid

Three multicenter prospective studies have provided evidence of the clinical validity of a bronchial genomic classifier in current or former cigarette smokers undergoing bronchoscopy for suspicion of lung cancer. The most recent study was a 3-cohort study that validated the second generation Percepta GSC test in an independent sample set. High sensitivity with modest specificity for the rule-out portion of the classifier, and high specificity with modest sensitivity for the rule-in portion was confirmed.

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 (RCTs).

No evidence directly demonstrating improved outcomes in patients managed with the Percepta GSC or BGC 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 the Percepta GSC in individuals with indeterminate bronchoscopy results for suspected lung

cancer change clinical management (in this case, reduction of invasive procedures)? and (2) Do those management changes improve outcomes?

Changes in Management

The clinical setting in which Percepta GSC is meant to be used is not well-defined: individuals who are suspected to have cancer but who have a nondiagnostic bronchoscopy.

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. Ferguson et al (2016) reported on the impact of the Percepta BGC on physician decision making for recommending invasive procedures among patients with an inconclusive bronchoscopy.[16] The results revealed that a negative (low-risk) result might reduce invasive procedure recommendations in patients diagnosed with benign disease.

Lee et al (2021) provided additional data on the effect of Percepta BCG on clinical management decisions among patients (N=283) with low or intermediate-risk lung nodules who had at least 1 year of follow-up.[17] The availability of Percepta results led to 34.3% of patients having their risk of malignancy downgraded. Two-thirds of these patients switched from a planned invasive procedure to surveillance.

Improved Outcomes

Indirect evidence suggests that use of the Percepta GSC has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. Compared with the standard care plan, some patients without cancer will have avoided an unnecessary invasive procedure, which is weighed against the small increase in missed cancers in patients who had cancer but tested as negative (low-risk) on the Percepta BGC.

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 be continued to be followed by active surveillance by low-dose CT imaging. In the context of lung cancers, overall survival depends on the 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 (eg, 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

Direct evidence of the clinical utility for GEP of bronchial brushings is lacking. Indirect evidence suggests that Percepta BGC 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.

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 and another lung nodule characterization test (REVEAL)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 (≤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 REVEAL validation study was a retrospective study that demonstrated use as a rule-out test in conjunction with the Veteran's Affairs (VA) Clinical Factors Model when the samples were considered inconclusive or intermediate risk by the VA model. The REVEAL model subsequently correctly identified 65% intermediate-risk samples as either low or high risk. The negative predictive value and sensitivity were both 94%. Limitations included a small sample size and use in conjunction with just 1 type of testing model. 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.

For individuals with undiagnosed pulmonary nodules following indeterminate bronchoscopy results for suspected lung cancer who receive gene expression profiling of bronchial brushings, the evidence includes multicenter prospective studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, hospitalizations, and resource utilization. A 3-cohort, prospective, multicenter study validated the second generation Percepta Genomic Sequencing Classifier (GSC) test in an independent sample set, showing high sensitivity for the rule-out portion of the classifier and high specificity for the rule-in portion of the classifier. For intermediate pretest risk patients with an inconclusive bronchoscopy, Percepta GSC can down-classify the risk of primary lung cancer to low with a 91% negative predictive value, or up-classify the risk to high with a 65% positive predictive value. Further assessment of clinical utility is warranted. Also, where the test would fall in the clinical pathway (ie, other than indeterminate bronchoscopy) is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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.[18]

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.[19] 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. [20,21,22]

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 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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

NCT03766958[a]	An Observational Registry Study to Evaluate the Performance of the BDX-XL2 Test	842	May 2024

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations

National:

There is no National Coverage Determination.

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

Coverage Indications, Limitations, and/or Medical Necessity
This Medicare contractor will provide limited coverage for the (BDX-XL2) test (Biodesix, Boulder, CO and Seattle, WA) for the management of a lung nodule, between 8 and 30mm in diameter, in patients 40 years or older, and with a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of 50% or less. 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. These lung nodules would then be candidates for non-invasive computed tomography (CT) surveillance instead of invasive procedures.

Coverage Summary
The BDX-XL2 assay is reasonable and necessary to assist physicians in the management of lung nodules by identifying those lung nodules with a high probability of being benign. This assay is only covered when the following conditions are met:

- Patient is at least 40 years of age and has a lung nodule of diameter 8 to 30mm, and
- The pre-test risk of cancer as determined by the Mayo risk prediction algorithm (10) is 50% or less

The intended use of the test is to assist physicians in the management of lung nodules by identifying those lung nodules with a high post-test probability of being benign. These lung nodules would then be candidates for non-invasive CT surveillance instead of invasive diagnostic procedures such as biopsy or surgery.

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): MolDX: Percepta® Bronchial Genomic Classifier (L37195)
Original Effective Date: 09/16/2017
Revision Effective Date: 10/26/2023

Coverage Indications, Limitations, and/or Medical Necessity
This Medicare contractor will provide limited coverage for the Percepta Bronchial Genomic Classifier (Veracyte, Inc., South San Francisco, CA) to identify patients with clinical low- or intermediate-risk of malignancy, after a non-diagnostic bronchoscopy, who may be followed with CT surveillance in lieu of further invasive biopsies or surgery. A patient's clinical risk of malignancy may be ascertained by the McWilliams or Gould risk assessment models. Coverage does not include clinical high risk patients or patients with known lung cancer.

Criteria for Coverage
Percepta BGC is covered only when the following clinical conditions 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 [3, 4] **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 as outlined below, **and**

Pre-Test Risk:	Post-Test Risk:	Post-Test Diagnostic Strategy
Intermediate	Intermediate	Proceed to further work up
Intermediate	Low Risk	CT surveillance
Low Risk	Low Risk	CT surveillance
Low Risk	Very Low Risk	CT surveillance

- Test is ordered by physician certified in Percepta Certification and Training Registry (CTR), **and**
- Patient is monitored for malignancy (suggested monitoring includes serial CT scans at 3 to 6, 9 to 12, and 18 to 24 months, using thin sections and non-contrast, low-dose techniques), **and**
- Physician will report outcomes in all risk groups including those monitored initially and those who undergo immediate intervention, **and**
- Clinical management is consistent with the post-test diagnostic strategy described above in ≥80% of tested patients.

Note: The Percepta BGC test should not be ordered if a physician does not intend to act upon the test result.

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

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 & Medicare 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

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24. Wisconsin Physicians Service Insurance Corporation, Local Coverage Determination (LCD): PERCEPTA© Bronchial Genomic Classifier (L37195), Original Effective Date: 09/16/17, Revision Effective Date: 10/26/2023.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/8/24, 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

Next Review Date: 3rd Qtr, 2025

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.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.