



# Louisiana

## Molecular Testing in the Management of Pulmonary Nodules

**Policy #** 00562

Original Effective Date: 08/23/2017

Current Effective Date: 08/15/2018

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers plasma-based proteomic screening including but not limited to Xpresys<sup>®±</sup> Lung in patients with undiagnosed pulmonary nodules detected by computed tomography to be **investigational**.\*

Based on review of available data, the Company considers gene expression profiling on bronchial brushings, including but not limited to Percepta<sup>®±</sup> Bronchial Genomic Classifier, in patients with indeterminate bronchoscopy results from undiagnosed pulmonary nodules to be **investigational**.\*

### **Background/Overview**

#### **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

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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.

Xpresys Lung 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 role of the test is to aid physicians in differentiating likely benign versus likely malignant nodules. If the test yields a likely benign result, patients may choose active surveillance via serial CT scans to monitor the pulmonary nodule. If the test yields a likely malignant result, invasive diagnostic procedures would be indicated. The test is therefore only used in the management of pulmonary nodules to rule in or out invasive diagnostic procedures and does not diagnose lung cancer.

### **GENE EXPRESSION PROFILING**

Gene expression profiling is the measurement of the activity of genes with cells. Messenger RNA (mRNA) 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 of clinical samples to assess for the risk for malignancy.

### **Gene Expression Profiling for an Indeterminate Bronchoscopy Result**

The Percepta Bronchial Genomic Classifier is a 23-gene gene expression profiling test that analyzes genomic changes in the airways of current or former smokers to assess a patient's risk of having lung cancer, without the direct testing of a pulmonary nodule. 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.

### **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

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 (Indi) and Percepta Bronchial Genomic 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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

There is no National Coverage Determination. In the absence of a National Coverage Determination, coverage decisions are left to the discretion of local Medicare carriers.

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### **Rationale/Source**

#### **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 relevant question addressed in this evidence review is: Does plasma-based proteomic screening appropriately eliminate or necessitate the need for invasive diagnostic procedures and lead to improved health outcomes?

The following PICOTS were used to select literature to inform this review.

##### ***Patients***

The relevant population of interest includes individuals with undiagnosed pulmonary nodules. In particular, as outlined in the evidence-based 2013 American College of Chest Physicians (ACCP) Guidelines on the diagnosis and management of lung cancer, decision-making about a single indeterminate lung nodule 8 to 30 mm on 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. Therefore, additional information in the segment of patients with an indeterminate lung nodule, 8 to 30 mm in diameter would be particularly useful.

##### ***Interventions***

The relevant intervention of interest is plasma-based proteomic screening. A particular focus was the Xpresys Lung test, which was the only commercially available test identified.

##### ***Comparators***

The relevant comparator of interest is standard clinical management 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 malignancy.

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### **Timing**

The time frame for evaluating performance of the test varies the time from 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.

### **Setting**

The primary setting would be in outpatient pulmonology or primary care offices.

### **Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

### **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).

Pecot et al (2012) validated a 7-peak matrix-assisted laser desorption ionization mass spectrometry proteomic signature in 2 prospective cohorts of patients with 1 or more pulmonary nodules on chest CT (total N=379 [cohort A: n=265; mean nodule size, 31.2 mm; cohort B: n=114; mean nodule size, 19.4 mm]). The area under the curve for the matrix-assisted laser desorption ionization mass spectrometry score alone for cohort A was 0.64 (95% confidence interval [CI], 0.58 to 0.71) and for cohort B was 0.64 (95% CI, 0.52 to 0.75). For cohort A, adding the proteomic signature to clinical and chest CT data did not significantly improve prognostic value. For cohort B, however, prognostic ability improved when the proteomic signature was added to clinical and chest CT data, as measured by the integration discrimination improvement index (integration discrimination improvement, 20%;  $p < 0.001$ ). Similarly, in a subgroup of 100 nodules from 5 to 200 mm in diameter, the proteomic signature added prognostic value (integration discrimination improvement, 15%;  $p < 0.001$ ).

Two studies were identified that reported on the development and validation of slightly different versions of a plasma-based classifier test to predict malignancy (Xpresys Lung), one with 13 proteins and one with 11.

Li et al (2013) reported on the development and validation of the 13-protein version, proposed to differentiate benign from malignant pulmonary lung nodules. The test identifies classifier proteins likely modulated by a few transcription regulators (NF2L2, AHR, MYC, and FOS) associated with lung cancer and inflammation. The classifier was developed in a set of 143 serum samples from subjects with either benign or stage IA lung cancer, with a nodule size 4 to 30 mm. The test was locked and validated in a set of 52 benign and 52 tumor samples. Test characteristics are shown in Table 1. These results were independent of age, nodule size, or smoking history.

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Vachani et al (2015) reported on the validation of an 11-protein plasma classifier designed to identify likely benign lung nodules in a sample of 141 plasma samples associated with indeterminate pulmonary nodules 8 to 30 mm in diameter. This retrospective, blinded analysis evaluated existing samples. The 11 proteins in this assay were reported to be derived from the 13-protein sample in Li et al ([2013] above). 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 at 48% specificity. Additional sample diagnostic characteristics, selected to keep the study's target NPV of 90%, are shown in Table 1. 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.

**Table 1. Summary of Diagnostic Performance Studies for Proteomic Tests to Predict Malignancy**

Study	Prevalence, %	Cutoff Value	Sensitivity, %	Specificity, %	NPV, %	PPV, %
Li et al (2013)	15	0.60	71	44	90	18
	20	0.46	83	29	87	23
	25	0.42	90	27	89	29
Vachani et al (2015)	23.1	0.35	93.2	18.5	90.1	26
	23.1	0.34	93.7	18.5	90.1	25.6
	23.1	0.33	94.7	17.6	90.3	25.5

NPV: negative predictive value; PPV: positive predictive value.

Vachani et al (2015) reported on a multicenter prospective-retrospective study of patients with indeterminate pulmonary nodules. 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% 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.

### **Section Summary: Clinically Valid**

Clinical validation studies were identified for 2 proteomic classifiers, both of which appear to be related to the development and validation of closely related versions of the Xpresys test. In general, the classifier has been designed to have a high NPV. However, its clinical validity is uncertain given that studies have reported on slightly different versions of the test. Also, studies have not reported how it reclassifies patients relative to clinical classifiers regarding risk. Proteomic classifiers may aid in the clinical assessment of cancer risk for indeterminate pulmonary nodules.

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### **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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 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 high NPV in patients with undiagnosed pulmonary nodules detected by CT change clinical management (in this case, reduction of invasive procedures)? (2) Do those management changes improve outcomes relative to a clinical classifier?

### **Changes in Management**

The clinical setting in which a proteomic classifier with high NPV is used, is individuals with undiagnosed pulmonary nodules detected by CT.

Indirect evidence suggests that 32.0% of surgeries and 31.8% of invasive procedures (biopsy and/or surgery) on benign nodules could have been avoided, while 24.0% of patients with malignancy would have been triaged to CT surveillance.

### **Improved Outcomes**

Indirect evidence suggests that use of a proteomic classifier with high NPV has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease vs malignancy. Compared with 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 be

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continued to be followed by active surveillance using 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 of invasive procedures (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 high NPV has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease vs malignancy. However, stronger clinical validity data would be needed to rely on indirect evidence for clinical utility.

## **GENE EXPRESSION PROFILING OF INDETERMINATE BRONCHOSCOPY RESULTS**

### **Clinical Context and Test Purpose**

The purpose of gene expression profiling of 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 relevant question addressed in this evidence review is: Does gene expression profiling of bronchial brushings reduce the need for invasive diagnostic procedures and lead to improved health outcomes?

The following PICOTS were used to select literature to inform this review.

### ***Patients***

The relevant population of interest, according to the manufacturer, is individuals with physician-assessed low or intermediate pretest risk of malignancy who are current or former smokers with inconclusive bronchoscopy results for suspected lung cancer.

### ***Interventions***

The test being considered is gene expression profiling of bronchial brushings.

### ***Comparators***

The following practice is currently being used: standard clinical management without gene expression profiling. The management of patients with suspected lung cancer with 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. According to guidelines from the American College of Chest Physicians (2013), in patients with suspected lung cancer with a central lesion, bronchoscopy is recommended to confirm the diagnosis. If

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bronchoscopy results are nondiagnostic and there is still a suspicion of lung cancer remains, additional testing is recommended (grade 1B recommendation).

### **Outcomes**

The potential beneficial outcomes of primary interest are avoiding an unneeded invasive biopsy of a nodule that 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.

### **Timing**

The time frame for outcomes 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.

### **Setting**

The primary setting would be in outpatient pulmonology offices.

### **Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

### **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).

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. 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

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reported as a dichotomous score ( $\geq 0.65$  as cancer-positive,  $< 0.65$  as cancer-negative). The performance characteristics of the classifier in the training and test set are shown in Table 2.

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). 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 ( $< 10\%$ , 10-39%, 40-60%, 61-85%,  $> 85\%$ ). 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. After exclusions due to sample quality issues, loss to follow-up, lack of final diagnosis, or nonprimary 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 2. The classifier improved 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 ( $> 60\%$ ) risk of cancer pre-bronchoscopy.

**Table 2. Summary of Clinical Validity Studies for GEC to Predict Malignancy in Bronchial Samples**

Study	Population	AUC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Whitney et al (2015)	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)	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)

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Study	Population	AUC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
	Risk >60% (n=108)				84 (75 to 81)	38 (15 to 65)
	Risk unknown (n=19)				47 (21 to 73)	100 (40 to 100)

AUC: area under the curve; CI: confidence interval; GEC: gene expression classifier.

Vachani et al (2016) reported on rates of invasive procedures from AEGIS-1 and -2. 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.

### Section Summary: Clinically Valid

Two 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. For patients with intermediate-risk of lung cancer with a nondiagnostic, bronchoscopic examination, the NPV was 91%. However, there has been limited replication outside of a single trial group.

### 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 Percepta Bronchial Genomic Classifier (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.

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A chain of evidence was developed, which addresses two key questions: (1) Does use of the Percepta BGC in individuals with indeterminate bronchoscopy results for suspected lung cancer change clinical management (in this case, reduction of invasive procedures)? (2) Do those management changes improve outcomes?

### *Changes in Management*

The clinical setting in which Percepta BGC 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. The results revealed that a negative (low-risk) result might reduce invasive procedure recommendations in patients diagnosed with benign disease.

### *Improved Outcomes*

Indirect evidence suggests that use of the Percepta BGC has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease vs 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 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 of invasive procedures (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 gene expression profiling 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 vs 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.

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### SUMMARY OF EVIDENCE

For individuals with undiagnosed pulmonary nodules detected by computed tomography who receive plasma-based proteomic screening, the evidence includes a prospective cohort and prospective-retrospective studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, hospitalizations, and resource utilization. The commercially available tests have been designed to have a high negative predictive value of 90%, although studies have reported on slightly different versions. A single multicenter prospective-retrospective study revealed that 32% of surgeries and 31.8% of invasive procedures could have been avoided; however, 24.0% of patients with malignancy would have been triaged to computed tomography surveillance (false-negative). Studies have not reported how this proteomic screening reclassifies patients relative to clinical classifiers regarding risk. Indirect evidence has suggested that a proteomic classifier with high negative predictive value has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease vs malignancy. The evidence is insufficient to determine the effects of the technology on health outcomes.

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. Reported receiver operating characteristic curve values ranged from 0.74 to 0.81, with a negative predictive value of 91%. Among patients with a low and intermediate pretest probability of cancer with an inconclusive bronchoscopy, 77 (85%) patients underwent invasive diagnostic procedures. However, there was a relatively high number of missed cancers. No validation of the test in other populations was identified. Also, where the test would fall in the clinical pathway (ie, other than indeterminate bronchoscopy) is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

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# Louisiana

## Molecular Testing in the Management of Pulmonary Nodules

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### Policy History

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08/03/2017 Medical Policy Committee review

08/23/2017 Medical Policy Implementation Committee approval. New policy.

08/09/2018 Medical Policy Committee review

08/15/2018 Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 08/2019

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HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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