For Dates of service 07/10/2017 and after this Medical Policy is replaced by MolDX
For Dates of Service 03/13/17 and after for Percepta Bronchial Genomic Classifier please refer to MolDX; there is limited coverage.

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Molecular Testing in the Management of Pulmonary Nodules

Policy #: 644
Category: Laboratory

Latest Review Date: June 2017
Policy Grade: B

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Plasma-based proteomic screening and gene expression profiling of bronchial brushing are molecular tests available in the diagnostic workup of pulmonary nodules. To rule out malignancy, invasive diagnostic procedures such as computed tomography (CT)-guided biopsies, bronchoscopies, or video-assisted thoracoscopic are often required, but each carries procedure-related complications ranging from postprocedure pain to pneumothorax. Molecular diagnostic tests have been proposed to aid in risk-stratifying patients to eliminate or necessitate the need for subsequent invasive diagnostic procedures.

Pulmonary Nodules

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

Proteomics

Proteomics is the study of the structure and function of proteins. The study of the concentration, structure and other characteristics of proteins in various bodily tissues, fluids, and other materials have 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.

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 smokes following an indeterminate bronchoscopy result to determine subsequent management of pulmonary nodules (e.g., active surveillance or invasive diagnostic procedures), and does not diagnose lung cancer.

Policy:

Effective for dates of service on or after March 13, 2017 and prior to July 10, 2017:
Blue Advantage will treat **Plasma-based proteomic screening** including but not limited to **Xpresys® Lung** in patients with undiagnosed pulmonary nodules detected by computed tomography as a **non-covered benefit** and as **investigational.**

Effective for dates of service prior to March 13, 2017:
Blue Advantage will treat **Plasma-based proteomic screening** including but not limited to **Xpresys® Lung** in patients with undiagnosed pulmonary nodules detected by computed tomography as a **non-covered benefit** and as **investigational.**

Blue Advantage will treat **gene expression profiling** on bronchial brushings, including but not limited to **Percepta® Bronchial Genomic Classifier,** in patients with indeterminate bronchoscopy results from undiagnosed pulmonary nodules as a **non-covered benefit and as investigational.**

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Following is a summary of the key literature through March 30, 2017.

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 computed tomography (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 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.

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.

Analytic Validity
Analytic validity is the ability of a test to accurately and reliably measure the marker of interest. Measures of analytic validity include sensitivity (detection rate), specificity (1 - false-positive rate), reliability (repeatability of test results), and assay robustness (resistance to small changes in preanalytic or analytic variables).

Li et al (2015) described an integrated quantification (InteQuan) method to better control preanalytic and analytic variability compared to a quantification method using stable isotope-labeled standard peptides (SISQuan). Sixteen lung cancer biomarker candidates in human plasma samples in three assessment studies, using immunoaffinity depletion coupled with multiple reaction monitoring mass spectrometry was used. InteQuan performed better than SISQuan in precision in all three studies and tolerated a two-fold difference in sample loading. The three studies lasted over six months and encountered major changes in experimental settings. Plasma proteins in low nanogram per milliliter to low microgram per milliliter concentrations were measured with a median technical coefficient of variation of 11.9% using InteQuan. The corresponding median coefficient of variation using SISQuan was 15.3% after linear fitting.

Section Summary: Analytic Validity
The analytic validity of mass spectrometry has been demonstrated in a research setting and is expected to be high. However, direct evidence for the analytic validity of Xpresys Lung or other plasma-based proteomic screening tests used in patients with pulmonary nodules is lacking.

Clinical Validity
Pecot et al (2012) validated a seven-peak matix-assisted laser desorption ionization mass spectrometry (MALDI MS) proteomic signature in two prospective cohorts of patients with one 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 (AUC) for the MALDI 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 (IDI) index (IDI=20%, $p<0.001$). Similarly, in a subgroup of 100 nodules from 5 to 200 mm in diameter, the proteomic signature added prognostic value (IDI=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.

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. The analysis was a retrospective, blinded analysis of existing samples. The 11 proteins in this assay were reported to be derived from the 13-protein sample in Li et al (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	15%	0.60	71%	44%	90%	18%
	20%	0.46	83%	29%	87%	23%
	25%	0.42	90%	27%	89%	29%
Vachani et al	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; NSCLC: non-small cell lung cancer; PPV: positive predictive value.

In 2015, Vachani et al reported on a multicenter prospective-retrospective study of patients with indeterminate pulmonary nodules (IPNs). A plasma protein classifier was used on 475 patients with nodules 8 to 30 mm in diameter who had an invasive procedure to confirm 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. In comparison, a rate of 24.5% (95% CI, 16.2% to 34.4%) patients with malignancy routed to CT surveillance by standard clinical practice has been reported.

Section Summary: Clinical Validity

Clinical validation studies were identified for two proteomic classifiers, two 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. In addition, studies have not reported how it reclassifies patients relative to clinical classifiers in terms of risk. Proteomic classifiers may aid in the clinical assessment of cancer risk for indeterminate pulmonary nodules.

Clinical Utility

No evidence directly demonstrating improved outcomes in patients managed with the Xpresys Lung was identified.

Therefore, a chain of indirect evidence was developed, which addresses two 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 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 a 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 continued to be followed by active surveillance by low dose CT imaging. In the context of lung cancers, overall survival is dependent 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 (e.g. pneumothorax). However, reductions in unnecessary invasive procedures must be weighed against outcomes and harms associated with a missed diagnosis of lung cancer at earlier, more treatable stages.

Section Summary: Clinical Utility
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 versus malignancy. However, stronger clinical validity data is needed to make and 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 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 relevant question addressed in this evidence review is: Does gene expression profiling on 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, includes individuals with physician-assessed low or intermediate pre-test risk of malignancy who are current or former smokers with inconclusive bronchoscopy results for suspected lung cancer.

Interventions
The relevant intervention of interest is gene expression profiling of bronchial brushings.

Comparators
The relevant comparator of interest is standard clinical management without gene expression profiling. The management of patients with suspected lung cancer with who have an indeterminate bronchoscopy result is no entirely standardized. However, according it is likely that in standard practice many patients would have a surgical biopsy, transthoracic needle aspiration (TTNA), or other testing, depending on the location of the nodule. According to 2013 guidelines from the American College of Chest Physicians, in patients with suspected lung cancer with a central lesion, bronchoscopy is recommended to confirm the diagnosis. If bronchoscopy results are non-diagnostic 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 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.

Timing
The time frame for outcomes measures varies from 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.

Analytic Validity
In 2016, Hu et al reported on the analytic performance of GEP to characterize the stability of RNA in bronchial brushing specimens during collection and shipment, the analytical specificity (i.e., potentially interfering substances) as tested on blood, and genomic DNA and assay performance studies including intrarun, interrun, and interlaboratory reproducibility. RNA content within bronchial brushing specimens preserved in RNAprotect cell reagent is stable for up to 20 days at 4°C with no changes in RNA yield or integrity. Analytic sensitivity studies have demonstrated tolerance to variation in RNA input (157-243 ng). Analytic specificity studies using cancer-positive and cancer-negative samples mixed with either blood (up to 10% input mass) or genomic DNA (up to 10% input mass) have demonstrated no assay interference. The test is reproducible from RNA extraction through to Percepta test result, including variation across operators, runs, reagent lots, and laboratories (SD=0.26 for scores on >6-unit scale).

Section Summary: Analytic Validity
One published study has reported on the analytic performance on the Percepta Bronchial Genomic Classifier and included sample stability, reproducibility, analytic sensitivity, and analytic specificity. The analytic performance and reproducibility are expected to be high based, and, in the context of testing of clinical samples, is expected to yield accurate and reproducible results.

Clinical Validity
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 AEGIS trials (Airway Epithelium Gene Expression In the DiagnosiS of Lung Cancer), which were two prospective, observational, cohort studies (AEGIS-1, AEGIS-2), for current or former smokers undergoing bronchoscopy for suspected lung cancer. The details of the cohorts are described further with Silvestri et al, 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 out 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 2.

Silvestri et al (2015) reported on the diagnostic performance of the gene expression classifier developed in Whitney et al in a sample of 639 patients enrolled in two multicenter prospective studies (AEGIS-1, n=298; and 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%, 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. 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 randomly allocated 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 are not reported. For the subset of 272 patients with a nondiagnostic bronchoscopy, the classifier performance is presented by the pretest physician-predicted risk of cancer. For most of the subpopulations, there was a very high NPV. However, there were 13 false negatives, 10 of whom 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 (N)	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Whitney et al	Training set, entire population (n=299)	0.78 (0.73 to 0.82)	93%	57%		
	Training set, subset with non-diagnostic bronchoscopy (n=134)	0.78 (0.71 to 0.85)				
	Test set with non-diagnostic 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 non-diagnostic bronchoscopy, by pretest cancer probability risk: Risk (N)					
	<10% (n=61)				7% (1 to 24%)	100% (89 to 100%)
	10-60% (n=84)				40%	91%

					(27 to 55%)	(75 to 98%)
	>60% (n=108)				84% (75 to 81%)	38% (15 to 65%)
	Unknown (n=19)				47% (21 to 73%)	100% (40 to 100%)

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

In 2016, Vachani et al reported on rates of invasive procedures from AEGIS-1 and -2. In 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: Clinical Validity

Two multicenter prospective studies have provided evidence of the clinical validity for 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.

Clinical Utility

No evidence directly demonstrating improved outcomes in patients managed with the Percepta Bronchial Genomic Classifier (BGC) was identified. Therefore, a chain of indirect evidence was developed, which addresses 2 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, have 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.11

The results revealed that a negative (low risk) result may 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 versus malignancy. Compared to 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 is dependent 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 (e.g., pneumothorax). However, reductions in unnecessary invasive procedures must be weighed against outcomes and harms associated with a missed diagnosis of lung cancer at earlier, more treatable stages.

Section Summary: Clinical Utility
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 versus malignancy. However, long-term follow-up data is 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 (CT) who receive plasma-based proteomic screening, the evidence includes an analytic validity study as well as 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 (NPV) 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 CT surveillance (false-negative). Studies have not reported how it reclassifies patients relative to clinical classifiers in terms of risk. Indirect evidence has suggested that a proteomic classifier with high NPV has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with undiagnosed pulmonary nodules pulmonary nodules following indeterminate bronchoscopy results for suspected lung cancer who receive gene expression profiling of bronchial brushings, the evidence includes an analytic study and 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 NPV of 91%. Among patients with low and intermediate pretest probability of cancer with an inconclusive bronchoscopy, 77 (85%) patients underwent invasive diagnostic procedures. However, there were a relatively high number of missed cancers. No validation of the test in other populations was identified. In addition, where the test would fall in the clinical pathway (i.e., other than indeterminate bronchoscopy) is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
The American College of Chest Physicians (2013) has published evidence-based clinical practice guidelines on the diagnosis and management of lung cancer, including pulmonary nodules.

U**.S. Preventive Services Task Force Recommendations**
Not applicable.

Key Words:
Pulmonary nodules, Proteomics, Xpresys Lung, Gene Expression Profiling, Percepta BGC

Approved by Governing Bodies:
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, Seattle, WA) and Percepta® Bronchial Genomic Classifier (Veracyte, South San Francisco, CA) 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 this test.

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:
CPT Codes:

83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
84999	Unlisted chemistry procedure.

References:

1. Detterbeck FC, Lewis SZ, Diekemper R, et al. Executive summary: Diagnosis and management of lung cancer, 3rd ed: american college of chest physicians evidence-based clinical practice guidelines. Chest. 2013; 143(5 suppl):7S-37S.
2. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. May 2013; 143(5 Suppl):e93S-120S.
3. Hu Z, Whitney D, Anderson JR, et al. Analytical performance of a bronchial genomic classifier. BMC Cancer. Feb 26 2016; 16:161.
4. Li XJ, Hayward C, Fong PY, et al. A blood-based proteomic classifier for the molecular characterization of pulmonary nodules. Sci Transl Med. Oct 16 2013; 5(207):207ra142.
5. Li XJ, Lee LW, Hayward C, et al. An integrated quantification method to increase the precision, robustness, and resolution of protein measurement in human plasma samples. Clin Proteomics. 2015; 12(1):3.
6. Pecot CV, Li M, Zhang XJ, et al. Added value of a serum proteomic signature in the diagnostic evaluation of lung nodules. Cancer Epidemiol Biomarkers Prev. May 2012; 21(5):786-792.
7. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. May 2013; 143(5 Suppl):e142S-165S.
8. Silvestri GA, Vachani A, Whitney D, et al. A bronchial genomic classifier for the diagnostic evaluation of lung cancer. N Engl J Med. Jul 16 2015; 373(3):243-251. PMID 25981554
9. Vachani A, Hammoud Z, Springmeyer S, et al. Clinical utility of a plasma protein classifier for indeterminate lung nodules. Lung. Dec 2015; 193(6):1023-1027.
10. Vachani A, Pass HI, Rom WN, et al. Validation of a multiprotein plasma classifier to identify benign lung nodules. J Thorac Oncol. Apr 2015; 10(4):629-637.
11. Vachani A, Whitney DH, Parsons EC, et al. Clinical utility of a bronchial genomic classifier in patients with suspected lung cancer. Chest. Jul 2016; 150(1):210-218.
12. Whitney DH, Elashoff MR, Porta-Smith K, et al. Derivation of a bronchial genomic classifier for lung cancer in a prospective study of patients undergoing diagnostic bronchoscopy. BMC Med Genomics. May 06 2015; 8:18.

Policy History:

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Medical Policy Group, January 2018

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.