Molecular Testing in the Management of Pulmonary Nodules

Policy Number: 2.04.142
Last Review: 1/1/19
Origination: 7/2017
Next Review: 7/1/19

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Molecular Testing in the Management of Pulmonary Nodules. This is considered investigational.

When Policy Topic is covered
n/a

When Policy Topic is not covered
Plasma-based proteomic screening using Xpresys® Lung or similar assays in patients with pulmonary nodules detected by computed tomography is considered investigational.

Gene expression profiling on bronchial brushings using Percepta® Bronchial Genomic Classifier or similar assays in patients with indeterminate bronchoscopy results is considered investigational.

The EarlyCDT Lung for the early detection of lung cancer is considered investigational.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With pulmonary nodules</td>
<td>• Plasma-based proteomic screening</td>
<td>• Standard diagnostic workup of</td>
<td>• Overall survival</td>
</tr>
<tr>
<td>discovered by computed</td>
<td></td>
<td>pulmonary nodules</td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td>tomography</td>
<td></td>
<td></td>
<td>• Test accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hospitalizations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resource utilization</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With undiagnosed</td>
<td>• Gene expression profiling of</td>
<td>• Standard diagnostic workup of</td>
<td>• Overall survival</td>
</tr>
<tr>
<td>pulmonary nodules</td>
<td>bronchial</td>
<td>pulmonary nodules</td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
</tbody>
</table>
Plasma-based proteomic screening and gene expression profiling of bronchial brushing are molecular diagnostic tests available in the diagnostic workup of pulmonary nodules. To rule out malignancy, invasive diagnostic procedures such as CT-guided biopsies, bronchoscopies or video-assisted thoracoscopic are often required but each carry procedure-related complications ranging from post-procedure pain to pneumothorax. Molecular diagnostic tests have been proposed to aid in risk-stratifying patients to eliminate or necessitate the need for subsequent invasive diagnostic procedures.

For individuals with pulmonary nodules discovered by computed tomography who receive plasma-based proteomic screening, the evidence includes an analytic validity study, prospective cohort and prospective-retrospective studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, test validity, morbid events, hospitalizations and resource utilization. Studies revealed a negative predictive value (NPV) of 90% and positive predictive value (PPV) of 18-26%. 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). Additional randomized controlled studies are necessary to establish the impact of this testing in decreasing unnecessary invasive procedures or surgeries and concurrently decreasing cancer-related deaths. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with pulmonary nodules following indeterminate bronchoscopy results for suspected lung cancer, the evidence includes an analytic study and multicenter prospective studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, test validity, morbid events, hospitalizations and resource utilization. Reported receiver-operating-characteristic curve (AUC) ranged from 0.74 to 0.81 and a negative predictive value (NPV) of 91%. Among patients with low and intermediate pretest probability of cancer with an inconclusive bronchoscopy, 77 patients (85%) underwent invasive diagnostic procedures. Of the 77 patients, use of the classifier 21 of 42 (50%) could have potentially led to active surveillance instead of invasive testing. In 35 patients diagnosed with lung cancer, 31 (89%) had a true positive classifier result while 4 (11%) had a false-negative classifier result. Additional studies are necessary to establish the impact of this testing in decreasing unnecessary invasive procedures or surgeries and concurrently decreasing cancer-related deaths. The evidence is insufficient to determine the effects of the technology on health outcomes.
Background

**PULMONARY NODULES**

Pulmonary nodules are a common clinical problem that may be found as an incidental finding on a chest x-ray or CT scan or in the context of lung cancer screening studies of smokers. The primary question following detection of pulmonary nodules is the probability of malignancy, with subsequent management of pulmonary nodules based on various factors such as the radiographic characteristics of the pulmonary nodule (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 forego invasive diagnostic procedures. However, due to the low positive predictive value of pulmonary nodules detected radiographically, many unnecessary invasive diagnostic procedures and/or surgeries are performed to confirm or eliminate the diagnosis of lung cancer.

**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 of identifying and managing various diseases, including cancers. 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 proteins.

**PLASMA-BASED PROTEOMIC SCREENING FOR PULMONARY NODULES**

Plasma-based proteomic screening is a molecular test that may help physicians 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 allowing for 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 (MRM-mass spec). The role of the test is to aid physicians in differentiating likely benign versus likely malignant nodules in patients. 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 rule-out for invasive diagnostic procedures and does not provide a diagnosis of lung cancer.
**GENE EXPRESSION PROFILING**
Gene expression profiling is the measurement of the activity of genes with cells. Messenger RNA (mRNA) serves as the bridge between DNA and functional proteins. Multiple molecular techniques such as Northern blots, ribonuclease protection assay, in-situ hybridization, spotted cDNA arrays, oligonucleotide arrays, reverse transcriptase PCR (RT-PCR) and transcriptome sequencing are used to 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 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 with cancer to assess a patient’s risk of having lung cancer, without the direct testing of a pulmonary nodule. The test is therefore only indicated for current and former smokes following an indeterminate bronchoscopy result to determine subsequent management of pulmonary nodules, eg active surveillance or invasive diagnostic procedures, and does not provide a diagnosis of lung cancer.

**REGULATORY STATUS**
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) 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 LDTs 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.

**EarlyCDT**
EarlyCDT (cancer detection test)–Lung measures a panel of six autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, Annexin 1, and SOX2) each selected for their involvement in the development of lung cancer. The test detects the body’s immune response in the form of antibodies to antigens, which are produced by solid tumor cancer cells. In healthy individuals, the immune system does not produce antibodies against normal tissue antigens. When cancer develops, cancer cells produce antigens that are abnormal or in some way modified from those found in normal tissue. The immune system detects these antigens and reacts by producing an abundance of autoantibodies that circulate in the bloodstream. As these autoantibodies form and circulate in the body during stages I and II, the earliest stages of lung cancer, their measurement signifies the presence of cancerous cells, indicating that a tumor exists.

Risk assessment and early detection of lung cancer in asymptomatic high-risk patient populations are the primary benefits of EarlyCDT-Lung. It is also used as a follow-up test for high-risk patients who have indeterminate lung nodules identified by CT.
**Rationale**

This evidence review was created in May 2017 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through March 6, 2018.

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.

**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 is individuals with undiagnosed pulmonary nodules. 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 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. 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 test being considered is plasma-based proteomic screening. Of particular focus is the Xpresys Lung test, which is the only commercially available test identified.
Comparators
The following practice is currently being used: 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 test performance varies from the initial CT scan to an invasive diagnostic procedure up to 2 years later, 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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence, %</th>
<th>Cutoff Value</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>NPV, %</th>
<th>PPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al (2013)³</td>
<td>15</td>
<td>0.60</td>
<td>71</td>
<td>44</td>
<td>90</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.46</td>
<td>83</td>
<td>29</td>
<td>87</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.42</td>
<td>90</td>
<td>27</td>
<td>89</td>
<td>29</td>
</tr>
<tr>
<td>Vachani et al (2015)⁴</td>
<td>23.1</td>
<td>0.35</td>
<td>93.2</td>
<td>18.5</td>
<td>90.1</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>23.1</td>
<td>0.34</td>
<td>93.7</td>
<td>18.5</td>
<td>90.1</td>
<td>25.6</td>
</tr>
<tr>
<td></td>
<td>23.1</td>
<td>0.33</td>
<td>94.7</td>
<td>17.6</td>
<td>90.3</td>
<td>25.5</td>
</tr>
</tbody>
</table>

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.

**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.\textsuperscript{5}

**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 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 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 bronchoscopy results are nondiagnostic and 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 reported as a dichotomous score (≥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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>AUC (95% CI)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitney et al (2015)⁷</td>
<td>Training set, entire population (n=299)</td>
<td>0.78 (0.73 to 0.82)</td>
<td>93</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Training set, subset with nondiagnostic bronchoscopy (n=134)</td>
<td>0.78 (0.71 to 0.85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test set with nondiagnostic bronchoscopy (n=123)</td>
<td>0.81 (0.73 to 0.88)</td>
<td>92 (78 to 98)</td>
<td>53 (42 to 63)</td>
<td>47 (36 to 58)</td>
<td>94 (83 to 99)</td>
</tr>
<tr>
<td>Silvestri et al (2015)⁸</td>
<td>AEGIS-1 (n=298)</td>
<td>0.78 (0.73 to 0.83)</td>
<td>88 (83 to 95)</td>
<td>47 (37 to 58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AEGIS-2 (n=341)</td>
<td>0.74 (0.68 to 0.80)</td>
<td>89 (84 to 92)</td>
<td>47 (36 to 59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subset of all patients with nondiagnostic bronchoscopy, by pretest cancer probability risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk &lt;10% (n=61)</td>
<td></td>
<td>7 (1 to 24)</td>
<td>100 (89 to 100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk 10%-60% (n=84)</td>
<td></td>
<td>40 (27 to 55)</td>
<td>91 (75 to 98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk &gt;60% (n=108)</td>
<td></td>
<td>84 (75 to 81)</td>
<td>38 (15 to 65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk unknown (n=19)</td>
<td></td>
<td>47 (21 to 73)</td>
<td>100 (40 to 100)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 -2.⁹ 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.

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.

**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.

Supplemental Information

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, which is discussed in the patient population parameters in the Plasma-Based Proteomic Screening Of Pulmonary Nodules section.11

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

Medicare National Coverage
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.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in April 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

References

Billing Coding/Physician Documentation Information

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

ICD-10 Codes
R91.1 Solitary pulmonary nodule

Additional Policy Key Words
EarlyCDT

Policy Implementation/Update Information

7/1/17 New Policy. Considered Investigational.
1/1/18 No policy statement changes.
7/1/18 No policy statement changes.
1/1/19 No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.