DRAFT Medical Coverage Policy | Molecular Testing in the Management of Pulmonary Nodules

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OVERVIEW
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 videoassisted 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 riskstratifying patients to eliminate or necessitate the need for subsequent invasive diagnostic procedures.

MEDICAL CRITERIA
Not applicable.

PRIOR AUTHORIZATION
Not applicable.

POLICY STATEMENT
BlueCHiP for Medicare and Commercial
Plasma-based proteomic screening including but not limited to Xpresys® Lung in patients with undiagnosed pulmonary nodules detected by computed tomography is considered not medically necessary as the evidence is insufficient to determine the effects of the
technology on health outcomes

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 is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes

COVERAGE
Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

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

PROTEOMICS

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

Plasma-Based Proteomic Screening for Pulmonary Nodules

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

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 (eg, active surveillance or invasive diagnostic procedures), and does not diagnose lung cancer.

SUMMARY OF EVIDENCE

For individuals with undiagnosed pulmonary nodules detected by 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 (ie, other than indeterminate bronchoscopy) is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes

REGULATORY STATUS

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

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.13

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov in April 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

CODING

There are not any specific codes for these tests and claims should be submitted with 84999-Unlisted chemistry procedure.

RELATED POLICIES

None

PUBLISHED

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REFERENCES:

1. 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 evidencebased clinical practice guidelines. Chest. May 2013;143(5 Suppl):e93S-120S. PMID 23649456
2. 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. PMID 25838814
3. 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. PMID 22374995
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. PMID 24132637
5. 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. PMID 25590604
6. 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. PMID 26376647
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. PMID 23649436

8. Hu Z, Whitney D, Anderson JR, et al. Analytical performance of a bronchial genomic classifier. BMC Cancer. Feb 26 2016;16:161. PMID 26920854
9. 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. PMID 25944280
10. 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
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. PMID 26896702
12. Ferguson JS, Van Wert R, Choi Y, et al. Impact of a bronchial genomic classifier on clinical decision making in patients undergoing diagnostic evaluation for lung cancer. BMC Pulm Med. May 17 2016;16(1):66. PMID 27184093
13. 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.