BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.142 Molecular Testing in the Management of Pulmonary Nodules

Effective Policy Date: October 1, 2023

Original Policy Date: June 2019

Related Policies:

None

Molecular Testing in the Management of Pulmonary Nodules

Description

Description

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-guided biopsies, bronchoscopies, or video-assisted thoracoscopic procedures are often required, but each carry 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.

Proteomics

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

Plasma-Based Proteomic Screening for Pulmonary Nodules

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

Nodify XL2 (BDX-XL2) is a plasma-based proteomic screening test that measures the relative abundance of proteins from multiple disease pathways associated with lung cancer using an analytic technique called multiple reaction monitoring mass spectroscopy. The test helps physicians identify lung nodules that are likely benign or at lower risk of cancer. If the test yields a "likely benign" or "reduced risk" result, patients may choose active surveillance via serial CT scans to monitor the pulmonary nodule. Earlier generations of the Nodify XL2 test include Xpresys Lung® and Xpresys Lung 2®.

Nodify CDT® is a proteomic test that uses multi-analyte immunoassay technology to measure autoantibodies associated with tumor antigens. The test helps physicians identify lung nodules that are likely malignant or at higher risk of cancer. Patients with a "high level" Nodify CDT test result have a higher risk of malignancy than predicted by clinical factors alone; invasive diagnostic procedures would be indicated in these cases.

The Nodify XL2 and Nodify CDT tests are therefore only used in the management of pulmonary nodules to rule out or rule in, invasive diagnostic procedures; they do not diagnose lung cancer. These tests are offered together as Biodesix's Nodify Lung® testing strategy, but physicians may also choose to order each test independently.

Gene Expression Profiling

Gene expression profiling (GEP) is the measurement of the activity of genes within cells. Messenger RNA serves as 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 GEP. An important role of GEP in molecular diagnostics is to detect cancer-associated gene expression in clinical samples to assess the risk for malignancy.

Gene Expression Profiling for an Indeterminate Bronchoscopy Result

The first generation Percepta® Bronchial Genomic Classifier was a 23-gene, GEP test that analyzed genomic changes in the airways of current or former smokers to assess a patient's risk of having lung cancer, without direct testing of a pulmonary nodule. This classifier was designed to be a "rule-out" test for intermediate-risk patients. The second generation Percepta Genomic Sequencing Classifier was developed to serve as both a "rule-in" test and a "rule-out" test, thereby increasing its potential utility in improving risk stratification. The test is indicated for current and former smokers following an indeterminate bronchoscopy result to determine the subsequent management of pulmonary nodules (eg, active surveillance or invasive diagnostic procedures), and does not diagnose lung cancer.

OBJECTIVE

The objective of this evidence review is to determine whether (1) plasma-based proteomic screening in individuals with pulmonary nodules discovered by computed tomography or (2) gene expression profiling of bronchial brushings in individuals with pulmonary nodules following indeterminate bronchoscopy for suspected lung cancer appropriately eliminates or necessitates the need for invasive diagnostic procedures and improves the net health outcome.

POLICY STATEMENT

Plasma-based proteomic screening, including but not limited to BDX-XL2 (Nodify XL2), in individuals with undiagnosed pulmonary nodules detected by computed tomography is considered **investigational**.

Gene expression profiling on bronchial brushings, including but not limited to the Percepta Genomic Sequencing Classifier, in individuals with indeterminate bronchoscopy results from undiagnosed pulmonary nodules is considered **investigational**.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Xpresys Lung 2, now Nodify XL2 (BDX-XL2; Integrated Diagnostics [Indi], purchased by Biodesix); Nodify CDT (Biodesix); and Percepta Genomic Sequencing Classifier (Veracyte) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

RATIONALE

Summary of Evidence

For individuals with undiagnosed pulmonary nodules detected by computed tomography (CT) who receive plasma-based proteomic screening, the evidence includes prospective cohorts and prospective-retrospective studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, hospitalizations, and resource utilization. Clinical validation studies were identified for 2 versions (Xpresys Lung, and Xpresys Lung version 2 [now Nodify XL2]) of a proteomic classifier. This classifier has undergone substantial evolution, from a 13-protein assay to a 2-protein assay integrated with clinical factors. Because of this evolution, the most relevant studies are with the most recent version 2 (Xpresys Lung version 2 [now Nodify XL2]). One validation study on version 2 has been identified. The classifier has been designed to have high specificity for malignant pulmonary nodules, and the validation study showed a specificity of 97% for patients with a low-to-moderate pretest probability (≤50%) of a malignant pulmonary nodule. The primary limitation of this study is that a high number of patients were excluded from the study due to incomplete clinical data or because they were subsequently determined to be outside of the intended use population. It is unclear if the intended use population was determined a priori. Validation in an independent sample in the intended use population is needed. No recent clinical validation studies were identified for the Nodify CDT test or the Nodify Lung testing strategy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Chest Physicians

In 2013, the American College of Chest Physicians published evidence-based clinical practice guidelines on the diagnosis and management of lung cancer, including pulmonary nodules, which is discussed in the patient population parameters in the 'Plasma-Based Proteomic Screening Of Pulmonary Nodules' section.[16,]

American Thoracic Society

In 2017, the American Thoracic Society published a position statement on the evaluation of molecular biomarkers for the early detection of lung cancer.[17,] The Society states that "a clinically useful molecular biomarker applied to the evaluation of lung nodules may lead to expedited therapy for early lung cancer and/or fewer aggressive interventions in patients with benign lung nodules." To be considered clinically useful, a molecular diagnosis "must lead to earlier diagnosis of malignant nodules without substantially increasing the number of procedures performed on patients with benign nodules" or "fewer procedures for patients with benign nodules without substantially delaying the diagnosis of cancer in patients with malignant nodules."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for non-small cell lung cancer, small cell lung cancer, or lung cancer screening do not mention plasma-based proteomic screening testing or gene expression profiling as a potential diagnostic or screening tool.[18,19,20,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

Some plans will provide limited coverage for the BDX-XL2 test (Biodesix) for the management of a lung nodule between 8 and 30 mm in diameter, in patients at least 40 years of age and with a pre-test cancer risk of 50% or less, as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules. Per Biodesix, both the Nodify XL2 and Nodify CDT tests are $0 out of pocket for covered Medicare beneficiaries.[21,]

Some plans will provide limited coverage for the PERCEPTA Bronchial Genomic Classifier (Veracyte) to identify patients with clinical low- or intermediate-risk of malignancy, after a non-diagnostic bronchoscopy, who may be followed with CT surveillance in lieu of further invasive biopsies or surgery. A patient"s clinical risk of malignancy may be ascertained by the McWilliams or Gould risk assessment models. Coverage does not include clinical high risk patients or patients with known lung cancer. Per Veracyte, the PERCEPTA Genomic Sequencing Classifier test is covered by Medicare.[22,]

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 evidence-based clinical practice guidelines. Chest. May 2013; 143(5 Suppl): e93S-e120S. PMID 23649456
2. 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
3. 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): 629-37. PMID 25590604
4. Vachani A, Hammoud Z, Springmeyer S, et al. Clinical Utility of a Plasma Protein Classifier for Indeterminate Lung Nodules. Lung. Dec 2015; 193(6): 1023-7. PMID 26376647
5. Kearney P, Hunsucker SW, Li XJ, et al. An integrated risk predictor for pulmonary nodules. PLoS One. 2017; 12(5): e0177635. PMID 28545097
6. Silvestri GA, Tanner NT, Kearney P, et al. Assessment of Plasma Proteomics Biomarker's Ability to Distinguish Benign From Malignant Lung Nodules: Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial. Chest. Sep 2018; 154(3): 491-500. PMID 29496499
7. Tanner NT, Springmeyer SC, Porter A, et al. Assessment of Integrated Classifier's Ability to Distinguish Benign From Malignant Lung Nodules: Extended Analyses and 2-Year Follow-Up Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial. Chest. Mar 2021; 159(3): 1283-1287. PMID 33171158

8. Vachani A, Pass HI, Rom Wn, et al. Validation of a multiprotein plasma classifier to identify benign lung nodules. Supplement. J Thorac Oncol. April 2015;10(4):629-637. https://cdn-links.lww.com/permalink/jto/a/jto_10_4_2015_01_07_massion_jto-d-14-00912_sdc1.pdf. Accessed April 1, 2022.
9. 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-e165S. PMID 23649436
10. 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
11. 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): 243-51. PMID 25981554
12. 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): 210-8. PMID 26896702
13. Mazzone P, Dotson T, Wahidi MM, et al. Clinical validation and utility of Percepta GSC for the evaluation of lung cancer. PLoS One. 2022; 17(7): e0268567. PMID 35830375
14. 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
15. Lee HJ, Mazzone P, Feller-Kopman D, et al. Impact of the Percepta Genomic Classifier on Clinical Management Decisions in a Multicenter Prospective Study. Chest. Jan 2021; 159(1): 401-412. PMID 32758562
16. 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. May 2013; 143(5 Suppl): 7S-37S. PMID 23649434
17. Mazzone PJ, Sears CR, Arenberg DA, et al. Evaluating Molecular Biomarkers for the Early Detection of Lung Cancer: When Is a Biomarker Ready for Clinical Use? An Official American Thoracic Society Policy Statement. Am J Respir Crit Care Med. Oct 01 2017; 196(7): e15-e29. PMID 28960111
18. National Comprehensive Cancer Network. NCCN Guidelines Version 2.2023: Non-Small Cell Lung Cancer. 2023; https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed March 13, 2023
19. National Comprehensive Cancer Network. NCCN Guidelines Version 3.2023: Small Cell Lung Cancer. 2023; https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed March 12, 2023.
20. National Comprehensive Cancer Network. NCCN Guidelines Version 1.2023: Lung Cancer Screening. 2023; https://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf. Accessed March 11, 2023.
21. Biodesix. Nodify Lung: Lung Nodule Management. 2023; https://www.biodesix.com/our-tests/nodify-lung. Accessed March 13, 2023.
22. Veracyte. Percepta Genomic Sequencing Classifier for your patients. 2023; https://lung.veracyte.com/percepta-gsc/for-your-patients/. Accessed March 13, 2023.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2019	New policy	Policy updated with literature review through March 26, 2019; references added. Plasma-based proteomic screening and Gene expression profiling on bronchial brushings considered investigational.
September 2020	Replace policy	Policy updated with literature review through March 9, 2020; reference added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through March 18, 2021; reference added. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through April 1, 2022; references added. Policy statements unchanged.
September 2023	Replace policy	Policy updated with literature review through March 10, 2023; references added. Minor editorial refinements to policy statements, intent unchanged.