PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

MEDICAL POLICY – 2.04.515

Plasma-based Proteomic Screening in the Management of Pulmonary Nodules

BCBSA Ref. Policy:	2.04.142	
Effective Date:	Aug. 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	July 8, 2024	None
Replaces:	12.04.142	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

Clicking this icon returns you to the hyperlinks menu above.

Introduction

A pulmonary nodule is a growth in the lung. Finding out if a nodule is benign (not harmful) or malignant (cancerous) often involves taking a sample of the nodule. Getting this sample requires an invasive procedure (invasive means something is put into the body). Depending on where the nodule is, the sample can be collected by passing a needle through the skin and chest wall into the lung or using a viewing instrument called a bronchoscope that's passed down the throat and into the lung's airways. When there is a strong suspicion of cancer, surgery can also be used to remove the nodule, and a sample is then examined to determine if cancer is present. Recently, tests have been developed that look at certain levels of proteins in the blood. The goal is to try to determine if invasive testing is needed for pulmonary nodules. These protein tests are investigational (unproven). More study is needed to determine if these tests are effective.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Service	Investigational
Plasma-based proteomic screening	**Plasma-based proteomic screening tests, including but not limited to Nodify XL2 (BDX-XL2), Nodify CDT, and REVEAL Lung Nodule Characterization (MagArray), in individuals with undiagnosed pulmonary nodules detected by computed tomography are considered investigational.**

Coding

Code	Description
CPT	
0080U	Oncology (lung), mass spectrometric analysis of aalectin-3-binding protein and scavenger receptor rysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy (Nodify XL2 [BDX-XL2])
0092U	Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy (Reveal Lung Nodule Characterization)
0360U	Oncology (lung), enzyme-linked immunosorbent assay (ELISA) of 7 autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, MAGE A4, and HuD), plasma, algorithm reported as a categorical result for risk of malignancy (Nodify CDT)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review

Description

Plasma-based proteomic screening is a molecular test 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 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 individuals to eliminate or necessitate the need for subsequent invasive diagnostic procedures.

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 (e.g., size, shape, density) and individual 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 individuals for invasive diagnostic procedures and ruling out individuals 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 individuals 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 individuals.

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, individuals 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.

REVEAL Lung Nodule Characterization is a plasma-protein biomarker test that may aid clinicians in characterizing indeterminate pulmonary nodules (4-30 mm) in current smokers 25 years of age and older. The test is based on a multianalyte assay with a proprietary algorithmic analysis using immunoassay, microarray, and magnetic nanoparticle detection techniques to obtain laboratory data for calculation of the risk score for lung cancer. The REVEAL Lung Nodule Characterization is presented on a scale from 0 to 100 with a single cut point at 50. The score is based on the measurement of 3 clinical factors (age, sex, and nodule diameter) and 3 proteins (epidermal growth factor receptor [EGFR], prosurfactant protein B [ProSB], and tissue inhibitor of

metalloproteinases 1 [TIMP1] associated with the presence of lung cancer. It may aid a clinician in the decision to perform a biopsy or to consider routine monitoring. It is not intended as a screening or stand-alone diagnostic assay.

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, retrospective studies, 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 two versions (Xpresys Lung, and Xpresys Lung version 2 [now Nodify XL2]) of a proteomic classifier and another lung nodule characterization test (REVEAL). The Nodify XL2 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 (Xpresys Lung version 2 [now Nodify XL2]). One validation study on version two 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 individuals 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 individuals 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 REVEAL validation study was a retrospective study that demonstrated use as a rule-out test in conjunction with the Veteran's Affairs (VA) Clinical Factors Model when the samples were considered inconclusive or intermediate risk by the VA model. The REVEAL model subsequently correctly identified 65% of intermediate-risk samples as either low or high risk. The negative predictive value and sensitivity were both 94%. Limitations included a small sample size and use in conjunction with just 1 type of testing model. Validation in an independent sample in the intended use population with additional probability models is needed. Indirect evidence suggests that a proteomic classifier with a high negative predictive value has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in **Table 1**.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04171492[a]	A Multicenter, Randomized Controlled Trial, Prospectively Evaluating the Clinical Utility of the Nodify XL2 Proteomic Classifier in Incidentally Discovered Low to Moderate Risk Lung Nodules	2000	Dec 2026
NCT03766958[a]	An Observational Registry Study to Evaluate the Performance of the BDX-XL2 Test	842	May 2024

NCT: national clinical trial. [a] Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion 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.[18]

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.[19] 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 as a potential diagnostic or screening tool.[20,21]

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 30mm 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.[22]

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 REVEAL Lung Nodule Characterization (MagArray, Inc.) 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 US Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

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 June 5, 2024.
9. Trivedi NN, Arjomandi M, Brown JK, et al. Risk assessment for indeterminate pulmonary nodules using a novel, plasma-protein based biomarker assay. Biomed Res Clin Pract. Dec 2018; 3(4). PMID 32913898
10. Pritchett MA, Sigal B, Bowling MR, et al. Assessing a biomarker's ability to reduce invasive procedures in patients with benign lung nodules: Results from the ORACLE study. PLoS One. 2023; 18(7): e0287409. PMID 37432960
11. 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
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. PMID 25944280
13. 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

14. 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

15. 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

16. 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

17. 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

18. 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

19. 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

20. National Comprehensive Cancer Network. NCCN Guidelines Version 3.2024: Non-Small Cell Lung Cancer. 2024; **https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf**. Accessed June 5, 2024.

21. National Comprehensive Cancer Network. NCCN Guidelines Version 2.2024: Small Cell Lung Cancer. 2023; **https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf**. Accessed June 5, 2024.

22. Biodesix. Nodify Lung: Lung Nodule Management. 2024; **https://www.biodesix.com/our-tests/nodify-lung**. Accessed June 5, 2024.

23. Veracyte. Percepta Genomic Sequencing Classifier for your patients. 2024; **https://lung.veracyte.com/percepta-gsc/for-your-patients/**. Accessed June 5, 2024.

History

Date	Comments
01/04/19	New policy, approved December 13, 2018, effective January 4, 2019. This policy replaces policy 12.04.142. Percepta Bronchial Genomic Classifier removed from policy.
05/01/19	Minor update, History section updated for clarity.
08/01/19	Annual Review, approved July 25, 2019. Policy updated with literature review through March 2019; references added. Name of proteomic plasma assay changed to BDX-XL2. Removed CPT code 84999. Added CPT codes 0080U (new code effective 1/1/19) and 0092U (new code effective7/1/19).
08/01/20	Annual Review, approved July 2, 2020. Policy updated with literature review through March 2020; reference added. Policy statements unchanged.
10/01/21	Annual Review, approved September 2, 2021. Policy updated with literature review through March 18, 2021; reference added. Policy statements unchanged.
08/01/22	Annual Review, approved July 11, 2022. Policy updated with literature review through April 1, 2022; references added. Policy statements unchanged.

Date	Comments
01/01/23	Coding update. Added new CPT code 0360U.
08/01/23	Annual Review, approved July 10, 2023. Policy updated with literature review through March 10, 2023; references added. Minor editorial refinements to policy statements, intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
08/01/24	Annual Review, approved July 8, 2024. Policy updated with literature review through March 27, 2024; references added. Policy statements updated to include the Nodify CDT and REVEAL Lung Nodule Characterization tests.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.