Molecular Testing in the Management of Pulmonary Nodules

Policy # 00562
Original Effective Date: 08/23/2017
Current Effective Date: 01/08/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider plasma-based proteomic screening BDX-XL2 (Nodify XL2®‡) in individuals with undiagnosed pulmonary nodules detected by computed tomography to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility will be considered when all of the following criteria are met:

- Lung nodule is between 8 and 30mm in diameter; AND
- Patient is 40 years or older; AND
- Pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules, see Policy Guidelines) is 50% or less; AND
- Test was not done before; AND
- Results will be used to assist in the management of lung nodules by identifying those lung nodules with a high probability of being benign and candidates for non-invasive CT surveillance instead of invasive procedures.

Based on review of available data, the Company may consider gene expression profiling Percepta®‡ Bronchial Genomic Classifier on bronchial brushings in individuals with indeterminate bronchoscopy results from undiagnosed pulmonary nodules to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility will be considered when all of the following criteria are met:

- Current or former smoker (>100 cigarettes in lifetime) age 21 and greater, with persistent undiagnosed pulmonary nodule; AND
- No prior or concurrent cancer; AND
- Physician-assessed low or intermediate pretest risk of lung cancer (see Policy Guidelines); AND
- Bronchoscopy is non-diagnostic, i.e., actionable benign or malignant diagnosis cannot be reached; AND
- Test was not done before and is performed on two brushings from the mainstem bronchus; AND
- Percepta®‡ BGC results will be utilized to determine whether CT surveillance is appropriate in lieu of further invasive biopsies or surgical procedures, e.g., low risk patients may be monitored with CT surveillance and avoid further invasive biopsies or surgical procedures.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers all other uses of BDX-XL2 (Nodify XL2), when criteria are not met, and other plasma-based proteomic screening tests (e.g., Nodify CDT) to be **investigational.***

Based on review of available data, the Company considers all other uses of Percepta®‡ Bronchial Genomic Classifier, when criteria are not met, and other bronchial genomic classifier tests to be **investigational.***

Policy Guidelines

The Mayo Clinic Model for Solitary Pulmonary Nodules for assessment of pre-test cancer risk can be found at this link: https://www.mdcalc.com/calc/4057/solitary-pulmonary-nodule-spn-malignancy-risk-score-mayo-clinic-model .

Physician-assessed low or intermediate pretest risk of malignancy is based on the following clinical characteristic stratification:

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Low Risk (<10%)
- Nodules < 10 mm; or
- < 10 pack/year smoking history

Intermediate Risk (10-50%)
- Nodules 10-30 mm; or
- 10-60 pack/year smoking history

High Risk (>60%)
- Nodules > 30 mm or irregular/spiculated margins; or
- > 60 pack/year smoking history

For nodules with the highest risk of lung cancer, recommendations include biopsy or surgical excision; tissue samples need to be sufficient and adequate to enable histology and molecular testing.

Background/Overview

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 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 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 measure 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 of clinical samples to assess for the risk for malignancy.

Gene Expression Profiling for an Indeterminate Bronchoscopy Result
The first generation Percepta®‡ Bronchial Genomic Classifier is a 23-gene, GEP 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. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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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 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.

Summary of Evidence

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.

For individuals with undiagnosed pulmonary nodules detected by computed tomography 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

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

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.

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. 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.

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.

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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished 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.

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22. Veracyte. Percepta Genomic Sequencing Classifier for your patients. 2023; https://lung.veracyte.com/percepta-gsc/for-your-patients/.

Policy History

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08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. New policy.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. No change to coverage.
06/10/2019	Coding update
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. New Assay was added to policy changing name of proteomic plasma assay from Xpresys to BDX- XL2.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Added REVEAL Lung Nodule Characterization as investigational.
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. No change to coverage.
03/03/2022	Medical Policy Committee review
03/09/2022	Medical Policy Implementation Committee approval. Removed Reveal Lung Nodule Characterization and BDX-XL2 (Nodify XL2) investigational statement.
12/01/2022	Medical Policy Committee review

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0080U, 0360U, 0395U, 81479, 81599, 84999 Add code effective 04/01/2022: 81554 Delete code effective 01/01/2023: 81554
HCPCS	No codes
ICD-10 Diagnosis	R911, R918, All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.