MEDICAL POLICY

POLICY TITLE	MOLECULAR TESTING IN THE MANAGEMENT OF PULMONARY NODULES
POLICY NUMBER	MP 2.375

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**3/1/2025**

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I. POLICY

Plasma-based proteomic screening, 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 is considered **investigational.** There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

Gene expression profiling on bronchial brushings, including but not limited to Percepta® Genomic Sequencing Classifier, in individuals with indeterminate bronchoscopy results from undiagnosed pulmonary nodules is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

Cross-reference:

MP 2.337 Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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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.

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 patient 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 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.

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.

REVEAL Lung Nodule Characterization (MagArray) is a plasma-protein biomarker test that may aid clinicians in characterizing indeterminate pulmonary nodules (4 to 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, prosurfactant protein B, and tissue inhibitor of metalloproteinases 1) 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.

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

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); REVEAL Lung Nodule Characterization (MagArray); 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.

IV. RATIONALE

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Summary of Evidence

For individuals with undiagnosed pulmonary nodules detected by computed tomography 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 2 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 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 (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 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.

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 (i.e., other than indeterminate bronchoscopy) is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational and therefore not covered:

Procedure Codes							
0080U	0092U	0360U	81479	84999			

IX. REFERENCES

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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*
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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*
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21. *National Comprehensive Cancer Network. NCCN Guidelines Version 2.2024: Small Cell Lung Cancer. 2023*
22. *Biodesix. Nodify Lung: Lung Nodule Management. 2024*
23. *Veracyte. Percepta Genomic Sequencing Classifier for your patients. 2024*
24. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.142, Molecular Testing in the Management of Pulmonary Nodules. June 2024*

X. POLICY HISTORY

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MP 2.375	**08/26/2020 New policy.** Adopt BCBSA-Full adoption
	12/08/2021 Consensus Review. Updated FEP, background, and references. No changes to coding.
	12/01/2022 Administrative Update. New code 0360U effective 01/01/2023

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	12/29/2022 Consensus Review. Updated background and references. Added 81479 to coding table.
	07/10/2023 Consensus Review. No change to policy statement. Policy Variation language updated. Background and Rationale updated. References added.
	01/19/2024 Administrative Update. Clinical benefit added.
	09/30/2024 Consensus Review. No change to policy statement. Background and Rationale updated. References added.
	01/24/2025 Administrative Update. Removed NCCN statement.

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