Molecular Testing in the Management of Pulmonary Nodules

Policy # 00562
Original Effective Date: 08/23/2017
Current Effective Date: 01/01/2023

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:

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- 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 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


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.

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 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. 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.

**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.

BDX-XL2 (Nodify® 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 role of the test is to aid physicians in differentiating likely benign from 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.

**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 Nodify XL2 (BDX-XL2; Integrated Diagnostics [Indi],

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Purchased by Biodesix) and Percepta®‡ 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.

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**
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. Reported receiver operating characteristic curve values ranged from 0.74 to 0.81, with a negative predictive value of 91%. Among patients with a low and intermediate pretest probability of cancer with an inconclusive bronchoscopy, 77 (85%) patients underwent invasive diagnostic procedures. However, there was a relatively high number of missed cancers. No validation of the test in other populations was identified. 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.
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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 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. 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. 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 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
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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."

U.S. Preventive Services Task Force Recommendations
Not applicable.

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
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<tr>
<td>NCT04171492a</td>
<td>A Multicenter, Randomized Controlled Trial,</td>
<td>2000</td>
<td>Dec 2024</td>
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<tr>
<td></td>
<td>Prospectively Evaluating the Clinical Utility of the Nodify XL2</td>
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<td></td>
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<tr>
<td></td>
<td>Proteomic Classifier in Incidentally Discovered Low to Moderate Risk</td>
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<tr>
<td></td>
<td>Lung Nodules</td>
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<tr>
<td>NCT03766958a</td>
<td>An Observational Registry Study to Evaluate the Performance of the BDX-XL2</td>
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NCT: national clinical trial.  
* Denotes industry-sponsored or cosponsored trial.

References
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Policy History
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08/03/2017 Medical Policy Committee review
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.
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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
12/14/2022 Medical Policy Implementation Committee approval. Senate bill policy update. Coverage changed from investigational to eligible for coverage with criteria.
02/27/2023 Coding update
06/07/2023 Coding update

Next Scheduled Review Date: 12/2023

**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 2021 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:

<table>
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<tr>
<th>Code Type</th>
<th>Code</th>
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<td>Add code effective 04/01/2023: 0360U</td>
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<td>No codes</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>R911, R918, All related diagnoses</td>
</tr>
</tbody>
</table>

*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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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.