Molecular Testing in the Management of Pulmonary Nodules

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 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.

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 eliminate or necessitate the need for invasive diagnostic procedures and improve the net health outcome.

POLICY STATEMENT

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

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

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**BENEFIT APPLICATION**

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.

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

**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. Xpresys Lung 2 (BDX-XL2 (Integrated Diagnostics [Indi], purchased by Biodesix) and Percepta Bronchial Genomic Classifier (Veracyte) are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**RATIONALE**

**Summary of Evidence**

For individuals with undiagnosed pulmonary nodules detected by CT who receive plasma-based proteomic screening, the evidence includes prospective cohorts and prospective-retrospective studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbidity events, hospitalizations, and resource utilization. Clinical validation studies were identified for two 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 two. One validation study on the 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 patients with 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 the effects of the technology on health outcomes.

For individuals with undiagnosed pulmonary nodules following indeterminate bronchoscopy results for suspected lung cancer who receive GEP of bronchial brushings, the evidence includes multicenter prospective studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbidity events, hospitalizations, and resource utilization. Reported receiver operating characteristic curve values ranged from 0.74 to 0.81, with an NPV 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 the effects of the technology on health outcomes.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Chest Physicians

The American College of Chest Physicians (2013) has 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. 12

American Thoracic Society

The American Thoracic Society (2017) published a position statement on the evaluation of molecular biomarkers for the early detection of lung cancer. 5 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."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

MolDX will provide limited coverage for the BDX-XL2 test (Biodexis) 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.

REFERENCES


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

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<th>Date</th>
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<td>June 2019</td>
<td>New policy</td>
<td>Policy updated with literature review through March 26, 2019; references added. Plasma-based proteomic screening and Gene expression profiling on bronchial brushings considered investigational.</td>
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