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Corporate Medical Policy

Molecular Testing of Pulmonary Specimens AHS - M2160

File Name:	molecular_testing_of_pulmonary_specimens
Origination:	1/1/2019
Last CAP Review:	3/2021
Next CAP Review:	3/2022
Last Review:	10/2021

Description of Procedure or Service

Pulmonary nodules are well-defined lesions found in lung tissue. These nodules are found on cross-sectional imaging and are frequently "incidental" (i.e. found on imaging not originally performed to identify the nodules). Assessment of malignancy risk is critical to managing these nodules, and a variety of tests have been used to accurately evaluate them. Some of these tests use cells obtained from bronchoscopies; these cells are purported to contain molecular markers indicative of malignancy. Evaluation of these cells has been used to determine malignancy risk of these nodules (Islam, 2018; Weinberger, 2020).

Related Policies:
Testing for Targeted Therapy of Non-Small-Cell Lung Cancer AHS - M2030

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Molecular testing of pulmonary specimens is considered not medically necessary for all applications.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Molecular Testing of Pulmonary Specimens is covered

Not applicable.

When Molecular Testing of Pulmonary Specimens is not covered

1. The use of gene expression profiling on bronchial brushings (e.g., including but not limited to Percepta Bronchial Genomic Classifier) is considered not medically necessary for all indications, including in patients with indeterminate bronchoscopy results from undiagnosed pulmonary nodules.

2. The use of genomic testing to improve the diagnosis of idiopathic pulmonary fibrosis (e.g. including but not limited to Envisia Genomic Classifier) is considered not medically necessary for all indications.

Policy Guidelines

In the United States, over 1.5 million lung nodules are detected annually (Kearney et al., 2017). These pulmonary nodules may arise due to a variety of conditions, some malignant (i.e. cancer), some benign (such as an infection). Since treatment varies widely between malignant and benign nodules, it is crucial to have well-validated and accurate methods to assess risk of malignancy. Traditionally, malignancy has been evaluated using a combination of factors, such as clinical, histological, and radiographic features. Once an initial assessment of malignancy has been performed, further management such as computed tomography (CT) surveillance or biopsy may follow. Low-dose computed tomography (LCDT) is the current standard for lung cancer screening. However, a limitation of the screening is that LCDT shows indeterminate pulmonary nodules which are not clearly defined as benign or cancerous. Assessment of a malignant nodule typically involves expensive biopsies whereas benign nodules may be only placed under close surveillance. Clinicians must often weigh the risk of a missed malignant diagnosis against performing an invasive procedure that may ultimately be unnecessary (Weinberger, 2020).

To address this population of indeterminate pulmonary nodules, some proprietary tests have been developed, such as Veracyte's Bronchial Genomic Classifier (Percepta). This test focuses on molecular analysis of the nodules, rather than clinical or radiographic analysis. The Percepta Bronchial Genomic Classifier uses cells collected during bronchoscopy to detect genomic changes indicative of a cancerous nodule. Percepta "is designed to reduce the number of invasive biopsies and other procedures that can follow when suspicious lung nodules are found on computerized tomography (CT) scans" (BU, 2015). Percepta purports that it can add diagnostic value without an invasive biopsy (Veracyte, 2017).

Another condition that may cause these pulmonary nodules is idiopathic pulmonary fibrosis (IPF). Although the cause is unknown by definition, clinical management of this condition may involve assessment of these nodules and further biopsy. Evaluation of these nodules includes several of the same procedures discussed above, such as clinical assessment, imaging, and pulmonary function tests. Diagnosis of IPF typically requires "exclusion of other known causes of interstitial lung disease (ILD) and either definite features of usual interstitial pneumonia (UIP) on high resolution computed tomography (HRCT) or certain combinations of HRCT and histopathologic features of UIP". Much debate exists around the role of the lung biopsy in diagnosis of IPF; authorities are conflicted on its importance in IPF assessment (King, 2019).

Veracyte has developed a genomic test named Envisia intended to aid physicians in differentiating between "idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILD), without having to do a surgical lung biopsy" (Veracyte, 2020). Envisia uses tissue samples obtained from a transbronchial biopsy and evaluates RNA of 190 genes purported to have common associations with fibrosis and inflammation. The results then report either "positive" or "negative" for usual interstitial pneumonia, considered to be the signature histopathologic pattern for IPF (G. Raghu, Mikacenic, Carmen, 2019; Veracyte, 2018).

Percepta is currently the only molecular test available for the assessment of pulmonary nodules that uses gene expression profiling. There are plasma-based proteomic tests that can be used to screen pulmonary nodules and estimate their risk of malignancy. Nodify XL2™ (previously called Xpresys Lung®, Xpresys Lung 2®, and BDX-XL2) is a plasma-based proteomic screening test that measures the abundance of proteins known to be related to lung cancer. Nodify XL2™ is reported to have a 90% negative predictive value (Ostrin, Sidransky, Spira, & Hanash, 2020). REVEAL Lung Nodule Characterization is a proteomic test for classification of pulmonary nodules in current smokers that calculates a risk score between 0 and 100 based on three clinical factors (smoking history, patient age, nodule size) and three blood proteins. REVEAL Lung Nodule Characterization is reported to have a sensitivity of 94% and a negative predictive value of 94% (Arfoosh et al., 2019). Lung Cancer Detector Test (LCDT1) is a proteomic test being developed for stage 1 non-small cell lung cancer detection. LCDT1 is expected to have 95.6% accuracy, 89.1% sensitivity, and 97.7% specificity (Goebel et al., 2020). EarlyCDT-Lung is a serum-based test that measures seven autoantibodies associated with lung cancer to estimate the risk of malignancy in small cell lung cancer and non-small cell lung cancer. EarlyCDT-Lung is reported to have 41% sensitivity and 87% specificity (Ostrin et al., 2020).

Analytical Validity

Hu et al. (2016) conducted studies to evaluate analytical performance of gene expression profiling test (Percepta test) using bronchial brushing specimens. The authors found that "analytical sensitivity studies demonstrated tolerance to variation in RNA input (157 ng to 243 ng). Analytical specificity studies utilizing cancer positive and cancer negative samples mixed with either blood (up to 10 % input mass) or genomic DNA (up to 10 % input mass) demonstrated no assay interference." The authors concluded that "analytical sensitivity, analytical specificity and robustness of the Percepta test were successfully verified, supporting its suitability for clinical use" (Hu et al., 2016).

Pankratz et al. (2017) aimed to develop a genomic classifier to distinguish usual interstitial pneumonia (UIP) from non-UIP in tissue samples obtained by transbronchial biopsy (TBB). The authors stated that this study was performed because UIP was the hallmark symptom of idiopathic pulmonary fibrosis (IPF) and imaging to identify UIP was frequently inconclusive. 283 samples from TBB were taken from 84 subjects, and "exome-enriched RNA sequencing" was performed on these samples. Then, a machine learning algorithm was created from 53 of these samples. This algorithm was then validated in the remaining 31 samples. The authors found that this algorithm distinguished UIP from non-UIP conditions with an area under curve (AUC) of 0.86 with a single sample. The sensitivity was found to be 63%, and the specificity was found to be 86%. The AUC improved to 0.92 when 3-5 TBB samples were included. The authors concluded that "genomic analysis and machine learning improves the utility of TBB for the diagnosis of UIP", but acknowledged that "this approach requires validation in an independent cohort of subjects before application in the clinic" (Pankratz et al., 2017).

Roncarati et al. (2020) evaluated the suitability of molecular testing for lung cancer assessment on bronchial washings. A novel droplet digital methylation-specific PCR (ddMSP) test was run on bronchial washings taken during fiber-optic bronchoscopy from 91 lung cancer patients and 31 control patients. The ddMSP assessed the aberrant methylenation status of four genes that "display aberrant methylation in more than 50% of cancer samples and no aberrant methylation in normal tissue." The ddMSP had a 97% sensitivity rate and 74% specificity. Additionally, DNA and RNA analysis of bronchial washings taken from 73 cancer patients and 14 noncancer patients found commonalities among mutations. The authors state that there is predictive value in mutation analysis but "frequent mutation detection in noncancer patients revealed the low specificity of this approach for diagnostic purposes." The authors concluded that molecular testing on bronchial washings "could be performed to support and complete the current clinical diagnostic/predictive strategies" (Roncarati et al., 2020).

Johnson et al. (2020) analyzed the performance of the Percepta Genomic Sequencing Classifier (GSC) in realistic conditions. Bronchial brushing samples were tested from bronchoscopy of patients with "suspicious lung nodules." The authors found no significant difference in Percepta GSC results with varying amounts of RNA input, 10% DNA contamination, and up to 11% blood RNA contamination. Additionally, results were reproducible between runs, within runs, and between laboratories. The authors concluded that "the analytical sensitivity, analytical specificity, and reproducibility of Percepta GSC laboratory results were successfully demonstrated under conditions of expected day to day variation in testing. Percepta GSC test results are analytically robust and suitable for routine clinical use" (Johnson et al., 2021).

Clinical Validity and Utility

Whitney et al. (2015) collected bronchial epithelial cells of 223 cancer-positive and 76 cancer-free subjects undergoing bronchoscopy for suspected lung cancer in a prospective, multi-center study. RNA from these samples was run on gene expression microarrays for training a gene-expression classifier. Out of the 232 genes whose expression levels in the bronchial airway were found to be associated with lung cancer, the authors built a classifier based on the combination of 17 cancer genes, gene expression predictors of smoking status, smoking history, and gender, plus patient age. The authors concluded that their gene classifier "is able to detect lung cancer in current and former smokers who have undergone bronchoscopy for suspicion of lung cancer. Due to the high NPV of the classifier, it could potentially inform clinical decisions regarding the need for further invasive testing in patients whose bronchoscopy is non-diagnostic" (Whitney et al., 2015).

Silvestri et al. (2015) reported on the diagnostic performance of a gene-expression classifier. 639 current or former smokers undergoing bronchoscopy for suspected lung cancer enrolled in two multicenter prospective studies (AEGIS-1 and AEGIS-2) were evaluated. A gene-expression classifier was measured in epithelial cells to assess the probability of lung cancer. In AEGIS-1, the classifier had a sensitivity of 88% and a specificity of 47%. In AEGIS-2, the classifier had a sensitivity of 89% and a specificity of 47%. The combination of the classifier plus bronchoscopy had a sensitivity of 96% in AEGIS-1 and 98% in AEGIS-2. The authors concluded that "the gene-expression classifier improved the diagnostic performance of bronchoscopy for the detection of lung cancer. In intermediate-risk patients with a nondiagnostic bronchoscopic examination, a negative classifier score provides support for a more conservative diagnostic approach" (Silvestri et al., 2015).

Ferguson et al. (2016) conducted a randomized, prospective decision impact survey study to evaluate pulmonologist recommendations in patients undergoing workup for lung cancer who had an inconclusive bronchoscopy. The authors' goal was to examine if a negative genomic classifier result that down-classifies a patient from intermediate risk to low risk (<10 %) for lung cancer would reduce the rate that physicians recommend more invasive testing among patients with an inconclusive bronchoscopy. The authors found that "invasive procedure recommendations were reduced from 57 % without the classifier result to 18 % with a negative (low risk) classifier result. Invasive procedure recommendations increased from 50 to 65 % with a positive (intermediate risk) classifier result." The authors concluded that their results "support the potential clinical utility of the classifier to improve management of patients undergoing bronchoscopy for suspect lung cancer by reducing additional invasive procedures in the setting of benign disease" (Ferguson et al., 2016).

Lee et al. (2017) published interim results from a large prospective registry of 665 patients undergoing diagnostic bronchoscopy. In a subset of 209 patients with an intermediate pretest risk of malignancy, Advanced bronchoscopic techniques were used in in 68% of cases. The BGC test results reclassified 74 patients as low risk. At 10 months post follow up the patients reclassified as low risk had a 40% relative reduction in the use of invasive procedures. The authors concluded that the BGC improves the sensitivity of diagnostic bronchoscopy for patients undergoing evaluation for lung cancer and can reduce the number if unnecessary invasive procedures (Feller-Kopman, Liu, Geisler, DeCamp, & Pietzsch, 2017).

Feller-Kopman et al. (2017) assessed the cost effectiveness of bronchoscopy plus a genomic classifier versus bronchoscopy alone in the diagnostic work-up of patients at intermediate risk for lung cancer. They found that "Use of the genomic classifier reduced invasive procedures by 28% at 1 month and 18% at 2 years, respectively. Total costs and QALY gain were similar with classifier use ($27,221 versus $27,183 and 1.512 versus 1.509, respectively), resulting in an incremental cost-effectiveness ratio of $15,052 per QALY". The authors concluded that use of a genomic classifier was associated with meaningful cost reduction in invasive procedures (Feller-Kopman et al., 2017).

Raghu et al. (2019) evaluated the prospective findings for the clinical validity and utility of a machine-learning based molecular test (Envisia). Findings from 90 patients were used to train the classifier, and then the authors attempted to validate the classifier in a set of 49 patients. The authors found that the classifier identified "usual interstitial pneumonia in transbronchial lung biopsy samples" in these 49 patients at 70% sensitivity and 88% specificity. 42 patients were noted to show "possible or inconsistent usual interstitial pneumonia on HRCT", and the classifier identified "underlying biopsy-proven usual interstitial pneumonia" at 81% positive predictive value. Clinical diagnoses based on histopathology data agreed with diagnoses based on classifier results at an 86% rate. The authors also found that diagnostic confidence was improved with addition of classifier results in 18 cases of idiopathic pulmonary fibrosis and all 48 patients with "non-diagnostic pathology or non-classifiable fibrosis histopathology" (63% vs 42%). The authors concluded that "The molecular test provided an objective method to aid clinicians and multidisciplinary teams in ascertaining a diagnosis of IPF, particularly for patients without a clear radiological diagnosis in samples that can be obtained by a less invasive method", noting that further studies were planned (G. Raghu et al., 2019).

D'Andrea et al. (2020) evaluated the cost-effectiveness of introducing a bronchial gene-expression classifier (BGC) to "improve the performance of bronchoscopy and the overall diagnostic process for early detection of lung cancer". The authors evaluated a cohort of former and current smokers with indeterminate pulmonary nodules and compared two different strategies: "(i) location-based strategy—integrated the

BGC to the bronchoscopy indication; (ii) simplified strategy—extended use of bronchoscopy plus BGC also on small and peripheral lesions". The authors modeled the following outcomes: "rate of invasive procedures, quality adjusted-life-years (QALYs), costs and incremental cost-effectiveness ratios". Both strategies were compared to the standard practice (defined as "bronchoscopy, transthoracic needle aspiration or biopsy (TTNA/B) or surgery, consistent with the current recommendations"). The location-based strategy reduced absolute rate of invasive procedures by 3.3% without increasing costs and resulted in savings when the classifier price was less than $3000. The simplified strategy reduced the absolute rate of invasive procedures by 10% and created an incremental cost-effectiveness ratio of $10109 per QALY. The authors concluded that both strategies reduced "unnecessary invasive procedures at high risk of adverse events" and that "the simplified use of BGC for central and peripheral lesions resulted in larger QALYs gains at acceptable cost". Finally, the authors noted that the location-based strategy is cost-saving if the classifier price declines (D'Andrea, Choudhry, Raby, Weinhouse, & Najafzadeh, 2020).

Lee et al. (2021) assessed the impact that Percepta results has on clinical management decisions. The authors conducted a prospective study on 283 patients with low- and intermediate-risk lung nodules across 35 centers in the US. In 35% of cases with a negative Percepta result, the risk of malignancy was down-classified. 79% of the down-classified cases changed their management plan to avoid an invasive procedure. Percepta down-classification did not significantly delay the time to diagnosis for patients with confirmed lung cancer. The authors concluded that "down-classification of nodule malignancy risk with the Percepta test decreased additional invasive procedures without a delay in time to diagnosis among those with lung cancer" (H. J. Lee et al., 2021).

Babiarz et al. (2021) tested the use of Percepta Genomic Atlas for identifying key molecular markers in surgical lung biopsy (SLB) specimens, transbronchial needle aspirates (TBNA), and bronchial brush specimens from an initial bronchoscopy at the time of diagnosis. DNA and RNA was extracted from Stage I, Stage II, and Stage III lung cancer SLB tissue. "Genomic alterations were observed in 65% of Stage I, 64% of Stage II and 73% of Stage III samples." TBNA and bronchial brush specimens were taken from 25 patients; multiple molecular alterations were detected in all patients. The authors concluded that "Percepta Genomic Atlas detects clinically actionable alterations in both SLB of early stage lung cancer tumors and in specimens collected at the time of diagnostic bronchoscopy or needle aspiration prior to surgery" (Babiarz et al., 2021).

Guidelines and Recommendations

American College of Chest Physicians (ACCP) (Detterbeck, Lewis, Diekemper, Addrizzo-Harris, & Alberts, 2013; Peter J. Mazzone et al., 2018; P. J. Mazzone et al., 2021)

In 2013, the ACCP published evidence-based clinical practice guidelines for diagnosis and management of lung cancer (Detterbeck et al., 2013). The guidelines did not mention gene expression profiling as a potential diagnostic or screening tool.

In 2018, the ACCP published guidelines for screening of lung cancer. In it, the ACCP comments that "Despite their potential promise, evidence that using such biomarkers would improve the efficiency of lung cancer screening is lacking. No applicable studies comparing molecular biomarkers vs NLST or USPSTF criteria were found that could be included in the systematic review for this guideline" (Peter J. Mazzone et al., 2018).

In 2021, the ACCP updated the guidelines for screening of lung cancer but did not change the recommendations on the use of biomarkers in lung cancer screening (P. J. Mazzone et al., 2021).

National Comprehensive Cancer Network (NCCN, 2020a, 2021a, 2021b)

The NCCN guidelines v5.2021 for Non-Small Cell Lung Cancer did not mention gene expression profiling as a potential diagnostic or screening tool (NCCN, 2021a).

The NCCN Guidelines v1.2022 for Small Cell Lung Cancer did not mention gene expression profiling as a potential diagnostic or screening tool (NCCN, 2021b).

The NCCN Guidelines v1.2021 for Lung Cancer Screening did not mention gene expression profiling as a potential diagnostic or screening tool (NCCN, 2020a).

European Society for Medical Oncology (ESMO) (Planchard et al., 2018; Postmus et al., 2017)

ESMO does not make any mention of gene expression profiling in its guideline for assessment of lung nodules (Postmus et al., 2017).

The EMSO Guidelines for metastatic non-small cell lung cancer recommends therapy-predictive biomarker testing after morphological diagnosis. Biomarker testing includes testing for *EGFR* mutation, *ALK* rearrangement, *ROS1* rearrangement, *BRAF* mutation, and PD-l1 expression. The guideline states that "this practice will be driven by the availability of treatments and will vary widely between different geopolitical health systems" (Planchard et al., 2018).

American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society (ATS/ERS/JRS/ALAT) (Ganesh Raghu et al., 2018)

This set of joint guidelines remarks that "Machine learning using molecular signatures is being developed to make a molecular diagnosis of UIP [usual interstitial pneumonia] in TBBx [transbronchial lung cryobiopsy] specimens but is not yet available in routine clinical practice. The guideline panel acknowledges that recent studies about the utility of molecular diagnostic tools that involve machine learning using TBBx samples are promising". The guidelines also note that further validation studies are pending (Ganesh Raghu et al., 2018).

European Paediatric Soft Tissue Sarcoma Study Group (Vaarwerk et al., 2019)

This study group published a report on the clinical significance of indeterminate pulmonary nodules in rhabdomyosarcoma. The group included 316 patients with non-metastatic rhabdomyosarcoma, 67 of which had indeterminate pulmonary nodules, 249 of which didn't have nodules. The authors found event-free survival and overall survival rates to be 77% and 82% respectively for patients with indeterminate nodules, and 73.2% and 80.8% respectively for patients without nodules. The authors concluded that their study "demonstrated that indeterminate pulmonary nodules at diagnosis do not affect outcome in patients with otherwise localized RMS. There is no need to biopsy or upstage patients with RMS who have indeterminate pulmonary nodules at diagnosis" (Vaarwerk et al., 2019).

Fleischner Society White Paper, Diagnostic Criteria for Idiopathic Pulmonary Fibrosis (Lynch et al., 2018)

This guideline focused on diagnostic criteria for IPF, including discussion on traditional features such as clinical, histopathological, and imaging factors. Under the "Areas of uncertainty" subheading, the Society comments that "we anticipate that molecular diagnosis with machine learning will play an increasing role in the diagnosis of IPF, particularly when integrated with clinical and imaging features" and emphasizes the importance of identifying molecular predictors of IPF (Lynch et al., 2018).

State and Federal Regulations, as applicable

These tests are considered laboratory developed tests (LDT); developed, validated and performed by individual laboratories. LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81479, 81554

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory panel 3/2021

Medical Director review 4/2021

Medical Director review 10/2021

Policy Implementation/Update Information

1/1/2019	New policy developed. Molecular testing/Gene expression profiling on bronchial brushings, including but not limited to Percepta Bronchial Genomic Classifier, is **considered investigational f**or all indications, including in patients with indeterminate bronchoscopy results from undiagnosed pulmonary nodules. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
10/1/19	Policy statement revised to read: Reimbursement is not allowed for the molecular testing of bronchial brushings is for all applications. "Investigational" changed to read "Reimbursement is not allowed…" Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019. (an)
12/10/19	Coding section updated per Avalon Q3 CAB review. No change to policy statement. (eel)
4/28/20	Specialty Matched Consultant Advisory Panel 3/31/2020. No change to policy statement. (eel)
11/10/20	Description, reference and policy guidelines sections updated per Avalon Q3 CAB review. Updated when not covered section for clarity. Title changed from "Molecular Testing of Bronchial Brushings" to "Molecular Testing of Pulmonary Specimens."(eel)
5/18/21	Specialty Matched Consultant Advisory Panel 3/2021. Medical Director review 4/2021. No change to policy statement. (bb)
8/24/21	Policy statement revised from "Reimbursement not allowed" to "not medically necessary". No change to policy intent. (jd)
11/16/21	Description and references updated by Avalon Q3 CAB review. Added code 81554. Related policies section added. No change to policy statement. Medical Director review 10/2021. (tt)