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Medical Policy

Subject:	**Bronchial Gene Expression Classification for the Diagnostic Evaluation of Lung Cancer**		
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Description/Scope

This document addresses gene expression classification for the diagnostic evaluation of lung cancer in individuals with suspected lung cancer following identification of pulmonary lesions on computed tomography (CT) scans. One commercially available test, the Percepta® Bronchial Genomic Classifier, evaluates the expression of 23 genes in bronchial brushing samples taken during bronchoscopy. The intention of the test is to improve the diagnostic performance of bronchoscopy and reduce the need for invasive diagnostic procedures.

Please refer to the documents indicated below for information regarding screening for lung cancer and managing pulmonary nodules:
ADMIN.00002 Preventive Health Guidelines
LAB.00111 Analysis of Proteomic Patterns

Position Statement

Investigational and Not Medically Necessary:

The use of bronchial gene expression classification for the diagnostic evaluation of lung cancer in individuals with pulmonary lesions is considered investigational and not medically necessary.

Rationale

The Percepta® Bronchial Genomic Classifier (Veracyte™, South San Francisco, CA), which analyzes 23 genes and age, is commercially available in the United States. The diagnostic performance of this bronchial

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genomic classifier for evaluating pulmonary lesions was evaluated prospectively by Silvestri and colleagues (2015). Development of the classifier was previously reported by Whitney (2015). The Silvestri publication reported on two cohorts of participants, known as the Airway Epithelial Gene Expression in the Diagnosis of Lung Cancer (AEGIS)-1 and AEGIS-2 studies. Both cohorts had the same eligibility criteria. They included current and former smokers (≥ 100 lifetime cigarettes) age 21 and over who were undergoing bronchoscopy to evaluate lesions suspected of being lung cancer. Individuals were followed until a diagnosis was made or until 12 months after bronchoscopy. If diagnosis of a benign condition or no specific diagnosis was made after 12 months, individuals were considered to be cancer-free.

The gene expression analysis was conducted using epithelial cell samples collected using cytology brushes during bronchoscopy. The same classifier algorithm was used in the two cohorts. Scores were reported as test-positive or test-negative based on a pre-specified threshold value. In addition, treating physicians reported each individual's pre-bronchoscopy likelihood of having lung cancer on a five-level scale (< 10%, 10 to 39%, 40 to 60%, 61 to 85% and > 85%).

A total of 855 participants in AEGIS-1 and 502 in AEGIS-2 met eligibility criteria and were enrolled in the study, although specimens from 155 individuals (11%) yielded insufficient or poor-quality RNA precluding measurement of the classifier. A total of 639 individuals in the AEGIS-1 and AEGIS-2 cohorts were included in the final analysis. Bronchoscopic examinations were non-diagnostic in 272 individuals (43%), including 120 of the 487 individuals (25%) in whom lung cancer was eventually diagnosed. The sensitivity of bronchoscopy for detecting lung cancer was 74% (95% confidence interval [CI], 68 to 79) in AEGIS-1 and 76% (95% CI, 71 to 81) in AEGIS-2. Of 267 with a non-diagnostic bronchoscopy, 170 (64%) underwent an invasive procedure for diagnostic purposes. Of these 170 individuals, 52 (31%) were diagnosed with benign lesions and 118 (69%) with lung cancer.

Diagnostic accuracy of the bronchial genomic classifier was similar in the two cohorts. In the AEGIS-1 cohort, the classifier accurately identified 194 of 220 individuals with lung cancer (sensitivity 88%; 95% CI, 83 to 92%) and 37 of 78 individuals without lung cancer (specificity 47%; 95% CI, 37 to 58%). In the AEGIS-2 cohort, the classifier correctly identified 237 of 267 individuals with lung cancer (sensitivity 89%; 95% CI, 84 to 92%) and 35 of 74 individuals without lung cancer (specificity 47%; 95% CI, 36 to 59%). When classifier results were combined with bronchoscopy findings, the sensitivity was 96% in AEGIS-1 and 98% in AEGIS-2, which was significantly higher than the sensitivity with bronchoscopy alone, p<0.001.

When the analysis was limited to individuals with a non-diagnostic bronchoscopy (n=272), the classifier accurately identified lung cancer in 49 of 57 individuals in AEGIS-1 (sensitivity 86%; 95% CI, 74 to 94%) and in 58 of 63 individuals in AEGIS-2 (sensitivity 92%; 95% CI, 82 to 97%). However, 13 individuals had a false negative classifier result (i.e., lung cancer and a negative classifier score). Of these, 10 individuals had a high (> 60%) pretest probability of lung cancer according to their treating physicians, and 3 had an intermediate (10-60%) pretest probability. The authors suggested that the classifier might be most useful in individuals with an intermediate pretest probability of cancer because the number of false negatives was small and this group would most likely undergo active surveillance which would likely identify any lesion growth, although active surveillance cannot be guaranteed in clinical practice.

Vachani and colleagues (2016) reported on subsequent invasive procedures obtained by participants in the AEGIS studies. The analysis included 188 individuals with a low or intermediate pretest probability of lung cancer who had an inconclusive bronchoscopy and had available data on additional procedures. Of these, 35 individuals were ultimately diagnosed with lung cancer and 153 had benign diagnoses. Of the 35 individuals who were diagnosed with lung cancer, 4 individuals had a negative classifier result, for a false negative rate of 11%. Of the 153 individuals with benign disease, 42 (27%) underwent subsequent invasive procedures. The classifier was negative (true negatives) in 21 of the 42 individuals (50%) who had invasive testing.

The potential impact of the Percepta bronchial genomic classifier on clinical decision-making was evaluated by Ferguson and colleagues (2016). This study compared board-certified pulmonologist's recommendations from case evaluation that either included or did not include classifier findings. Physicians were presented with case vignettes based on 36 participants in the AEGIS studies. About half of the cases included classifier information and these cases were presented in random order. A total of 202 physicians participated and completed 1523 case reviews on the 36 AEGIS participants. This included 787 (52%) cases assessed based on clinical information without classifier results and 736 (48%) cases assessed with clinical information plus the classifier results.

For cases with a negative classifier finding, physicians recommended invasive procedures in 57% of cases when provided only with clinical information on the case, compared with 18% when informed there was a negative classifier finding (p<0.001). For cases with positive classifier findings, the rate of recommending invasive procedures was 50% when provided only with clinical findings versus 65% when the positive classifier finding was also reported (p<0.001). As a secondary endpoint, the investigators examined the association between physician recommendations and the ultimate diagnosis. In the group with benign conditions the rate of invasive procedure recommendations was 54% when only provided with clinical

information and 41% when classifier results were provided (p<0.001). For malignant cases, the rate of recommending invasive procedures was 50% with clinical information only and 64% with classifier information (p=0.003). This study was not conducted in a clinical setting, and subsequent procedures and health outcomes were not assessed.

While publications on the AEGIS studies show that, with the Percepta bronchial genomic classifier, there is the potential for individuals with a non-diagnostic bronchoscopy to avoid unnecessary invasive procedures, no prospective, randomized application of the Percepta bronchial genomic classifier has been conducted to determine clinical utility or assess outcome data. Of note, the risk of a false-negative finding has the potential to delay diagnosis, resulting in poorer health outcomes. The performance of the Percepta bronchial genomic classifier outside of the clinical trial setting remains unknown.

The National Comprehensive Cancer Network (NCCN) guideline for lung cancer screening (V2.2019) has algorithms for evaluation of different types and sizes of nodules identified by low-dose CT screening. The guideline does not mention gene expression profiling or genomic bronchial profiling for evaluating nodules identified by screening.

Background/Overview

Lung and bronchus cancer is the third-most commonly diagnosed cancer in the United States and the most common cause of cancer mortality. In 2015, the incidence of new lung and bronchus cancer cases was 57.5 per 100,000 people and the mortality rate was 40.5 per 100,000 people (CDC, 2018). Lung cancer has a better prognosis when it is diagnosed at an earlier stage. For example, the 5-year survival rate of the most common form of lung cancer, non-small cell lung cancer (NSCLC), is 70-90% for stage 1 tumors (Blandin Knight, 2017). However, about 75% of individuals have advanced disease (Stage III/IV) at the time of diagnosis and a much less favorable prognosis.

Cigarette smoking is the leading risk factor for lung cancer (ACS, 2019). The risk increases as the length of time of smoking and the number of cigarettes increases. Screening current and former smokers with low-dose computed tomography (CT) was evaluated in the National Lung Screening Trial (NLST). The study included individuals who were between the ages of 55-74 with at least a 30 pack-year history of smoking and were current smokers or former smokers who had quit within the previous 15 years. The primary finding of

the study was that screening with low-dose CT significantly reduced the rate of lung cancer mortality compared with screening with chest radiography (NSLT Research Team, 2011).

Screening for lung cancer is currently recommended for high-risk individuals similar to NLST participants. In 2013, the U.S. Preventive Services Task Force (USPSTF, 2013) published an updated lung cancer screening guideline (Grade B) recommending:

> **…annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.**

With the increased availability of CT screening for lung cancer, an increased number of pulmonary nodules are being identified, many of which are false positives. A systematic review of evidence for the USPSTF (Humphrey, 2013) stated that between 9 and 51% of partisans had positive examinations in baseline screens and the positive predictive value (PPV) of these abnormal results ranged from 2 to 36%. Positive results, including false positives, require follow-up, which can include additional imaging, percutaneous needle biopsy and invasive procedures.

The NCCN has recommendations for evaluation of findings from lung cancer screening in their lung cancer screening guideline (V2. 2019). For solid nodules identified on an initial low-dose CT screen, when lesions are 15 mm or larger, a repeat low-dose CT in 3 months is recommended for individuals who have a low suspicion of cancer, and biopsy or surgical excision is recommended for individuals with a high suspicion of cancer. Determining risk of cancer involves multidisciplinary input and possibly use of a lung nodule risk calculator. For solid endobronchial nodules identified in screening with low-dose CT, a repeat low-dose CT is recommended and, if there is no resolution, bronchoscopy is recommended.

Several classifier tests have been developed to aid in the differentiation of benign and malignant pulmonary nodules. These include proteomic tests, such as the Xpresys™ Lung test, addressed in LAB.00011, and gene expression profiling tests. The Percepta® Bronchial Genomic Classifier (Veracyte) evaluates the expression of 23 genes in bronchial brushing samples taken during bronchoscopy. Classifier test results are intended to reduce the need for invasive diagnostic procedures for nodules identified on CT scans.

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Definitions

Bronchoscopy: An endoscopic test that utilizes either a rigid or flexible scope, in order to visualize and collect samples (washing, brushing, biopsy, culture, etc.) from the endobronchial tubes/branches of the respiratory system.

Computed tomography (CT): An imaging technique that creates multiple cross-sectional images of the body by using special x-rays and computer enhancement to detect disease or abnormalities.

Gene expression profiling: A laboratory test that measures the activity of multiple genes at once for diagnostic or prognostic purposes. The test result is often reported as a proprietary summary score.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
81479	**Unlisted molecular pathology procedure [when specified as a gene expression classifier for lung cancer, e.g., Percepta Bronchial Genomic Classifier]**
ICD-10 Diagnosis	
	All diagnoses, including but not limited to
R91.1	**Solitary pulmonary nodule**
R91.8	**Other nonspecific abnormal finding of lung field**

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Peer Reviewed Publications:

1. **Blandin Knight S, Crosbie PA, Balata H et al. Progress and prospects of early detection in lung cancer. Open Biol. 2017 Sep; 7(9).**
2. **Ferguson JS, Van Wert R, Choi Y et al. Impact of a bronchial genomic classifier on clinical decision making in patients undergoing diagnostic evaluation for lung cancer. BMC Pulm Med. 2016; 16(1):66.**
3. **National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011; 365(5):395-409.**
4. **Silvestri GA, Vachani A, Whitney D et al. AEGIS Study Team. A bronchial genomic classifier for the diagnostic evaluation of lung cancer. N Engl J Med. 2015; 373(3):243-51.**
5. **Vachani A, Whitney DH, Parsons EC et al. Clinical utility of a bronchial genomic classifier in patients with suspected lung cancer. Chest. 2016; 150(1):210-8.**
6. **Whitney DH, Elashoff MR, Porta-Smith K et al. Derivation of a bronchial genomic classifier for lung cancer in a prospective study of patients undergoing diagnostic bronchoscopy. BMC Med Genomics. 2015; 8:18.**

Government Agency, Medical Society, and Other Authoritative Publications:

1. **Centers for Disease Control and Prevention (CDC). United States Cancer Statistics: Data Visualizations. Available at: https://www.cdc.gov/cancer/uscs/index.htm, Accessed on April 11, 2019.**
2. **Gould MK, Donington J, Lynch WR et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e93S-e120S.**
3. **Humphrey L, Deffebach M, Pappas M et al. Screening for Lung Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 105. AHRQ Publication No. 13-05188-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2013. Available at: https://www.ncbi.nlm.nih.gov/sites/books/NBK154610/pdf/Bookshelf_NBK154610.pdf. Accessed on April 15, 2019.**
4. **NCCN Clinical Practice Guidelines in Oncology®. © 2018 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on April 8, 2019.**
    a. **Lung Cancer Screening (V2.2019). Revised August 27, 2018.**
5. **United States Preventive Services Task Force. Lung cancer screening. December 2013. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lung-cancer-screening?ds=1&s=lung cancer. Accessed on April 8, 2019.**

Websites for Additional Information

1. **American Cancer Society. Lung cancer screening guidelines. Available at: https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/lung-cancer-screening-guidelines.html. Accessed on April 11, 2019.**
2. **American Cancer Society. Lung cancer prevention and early detection. Last updated 2019. Available at: https://www.cancer.org/cancer/lung-cancer/prevention-and-early-detection.html. Accessed on April 11, 2019.**
3. **Centers for Disease Control and Prevention (CDC). Lung Cancer. Available at: https://www.cdc.gov/cancer/lung/. Accessed on April 11, 2019.**

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	06/06/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.