

## Molecular Testing of Pulmonary Specimens

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### I. Policy Description

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 pulmonary nodules, and a variety of tests have been used to accurately evaluate them. Some of these tests use gene expression profiling (GEP) on cells obtained from bronchoscopies, as these cells are purported to contain molecular markers indicative of malignancy (Islam, 2023; Weinberger, 2022). Other tests employ liquid biopsy and proteomic analysis to assign malignancy risk.

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown etiology that causes irreversible scarring (fibrosis) of the lung. Disease progression and increasing fibrosis often result in breathing difficulties that may subsequently lead to respiratory failure. IPF is a diagnosis of exclusion, and molecular tests are emerging as potentially useful tools that may help differentiate between IPF and other interstitial lung diseases (ILD).

### II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

- 1) For individuals with a suspicious pulmonary nodule (see Note 1), cancer risk assessment using Nodify XL2 proteomic analysis **MEETS COVERAGE CRITERIA** when **all** of the following conditions are met:
  - a) The pulmonary nodule size is 8-30 mm.
  - b) The patient is 40 years of age or older.
  - c) The pre-test risk of cancer is less than 50% based on the Solitary Pulmonary Nodule Malignancy Risk Score (Mayo Clinic Model).

*The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual’s illness.*

- 2) For all other indications, molecular testing for pulmonary disease **DOES NOT MEET COVERAGE CRITERIA**.

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## NOTES:

**Note 1:** While this is not considered a surgical procedure, it is recommended that individuals who are receiving this test should first undergo an informed consent process to discuss the benefits and risks of pursuing this test versus receiving a biopsy to rule lung cancer.

## III. Table of Terminology

Term	Definition
4MP	Four-marker protein panel
ACCP	American College of Chest Physicians
AEGIS	Airway Epithelial Gene Expression in the Diagnosis of Lung Cancer
ALAT	Latin American Thoracic Society
ALK	<i>Anaplastic lymphoma kinase</i>
ATS	American Thoracic Society
AUC	Area under curve
BGC	Bronchial Genomic Classifier
BRAF	<i>B-Raf proto-oncogene</i>
CA-125	Cancer antigen 125
CEA	Carcinoembryonic antigen
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid Services
CT	Computed tomography
CYFRA 21–1	Cytokeratin-19 soluble fragment
ddMSP	methylation-specific droplet digital PCR
EGFR	<i>Epidermal growth factor receptor</i>
ERS	European Respiratory Society
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GSC	Genomic Sequencing Classifier
HRCT	High resolution computed tomography
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
JRS	Japanese Respiratory Society
LCD	Local coverage determinations
LDCT	Low-dose computed tomography
LCDT1	Lung cancer detector test
LDT	Laboratory developed tests
LG3BP	Galectin-3-binding protein
MRM	Multiple reaction monitoring
mRNA	Messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
NLST	National Lung Screening Trial
NPV	Negative predictive value
NY-ESO-1	New York esophageal cancer-1 antibody
PANOPTIC	Pulmonary Nodule Plasma Proteomic Classifier
PCR	Polymerase chain reaction

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PLCO	Prostate lung colorectal ovarian
PPF	Progressive pulmonary fibrosis
QALY	Quality-adjusted life-years
RNA	Ribonucleic acid
<i>ROS1</i>	<i>ROS proto-oncogene 1, receptor tyrosine kinase</i>
SLB	Surgical lung biopsy
TBB	Transbronchial biopsy
TBBx	Transbronchial lung cryobiopsy
TBNA	Transbronchial needle aspirates
TTNA/B	Transthoracic needle aspiration or biopsy
UIP	Usual interstitial pneumonia
USPSTF	United States Preventive Services Task Force

#### IV. Scientific Background

In the United States, over 1.5 million lung nodules are detected annually (Kearney et al., 2017). These pulmonary nodules occur due to a variety of conditions, some malignant (i.e., cancer), and 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 (LDCT) is the current standard for lung cancer screening. However, a limitation of the screening is that LDCT shows indeterminate pulmonary nodules which are not clearly defined as benign or cancerous. Assessment of a potentially malignant nodule typically involves invasive biopsy whereas benign nodules may be only placed under surveillance. Clinicians must often weigh the risk of a missed malignant diagnosis against performing an invasive procedure that may ultimately be unnecessary (Weinberger, 2022).

Biomarkers are emerging as clinically useful tools in the management of pulmonary disorders. Validated biomarkers can potentially help improve risk-stratification, facilitate appropriate diagnosis, and may also reduce the number of invasive procedures that patients receive, and the morbidity associated with them.

##### **Proprietary Testing**

To assist in the classification and management of indeterminate pulmonary nodules, several proprietary tests have been developed, such as Veracyte’s Bronchial Genomic Classifier (Percepta BGC). This test focuses on molecular analysis of the nodules, rather than clinical or radiographic analysis. The Percepta BGC uses cells collected during bronchoscopy to detect genomic changes indicative of a cancerous nodule by analyzing the expression of twenty-three lung cancer associated genes in addition to patient age. Percepta BGC “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), and may improve the diagnostic performance of bronchoscopy in detecting lung cancer.

A second-generation risk stratification algorithm called Percepta Genomic Sequencing Classifier (GSC) was described by Choi et al. (2020), and suggested to have broadened utility beyond the BGC for

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pulmonary nodule management. The GSC considers 1232 gene transcripts coupled with specific clinical factors (gender, age, pack-year, inhaled medication, and specimen collection timing) to calculate the risk of primary lung cancer, and is indicated for use in patients with an inconclusive bronchoscopy result, who are current or former smokers, and have no prior history of cancer (Veracyte). A strength of the test is that it may be used in patients across several different pre-test risk categories of cancer, though the clinical validity measurements vary.

Veracyte has developed other tests that are undergoing validation to aid in the management of pulmonary nodules. These include the Percepta Nasal Swab, which is a genomic test that uses a sample from beyond the inferior nasal turbinate to evaluate a lung nodule's risk of malignancy, and the Percepta Genomic Atlas; an NGS-based assay that uses a tissue sample collected through bronchoscopy to identify genomic alterations in 54 genes, to help inform targeted therapy for confirmed malignancies (Babiarz et al., 2021; Veracyte, 2023b).

Another condition that is sometimes associated with pulmonary nodules is idiopathic pulmonary fibrosis (IPF). Although the cause of IPF is unknown, by definition, clinical management of this condition may involve assessment of any lung nodules that are present, and further biopsy. Evaluation of nodules associated with IPF 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, 2023).

Veracyte has developed a genomic test named Envisia intended to aid physicians in differentiating between "idiopathic pulmonary fibrosis (IPF) from other interstitial lung diseases (ILD), without the need for invasive, risky, and costly surgery" (Veracyte, 2023a). 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 (Raghu, 2023; Veracyte, 2018).

There are plasma-based proteomic tests that can be used to screen pulmonary nodules and estimate their risk of malignancy. Nodify XL2 (also known as Xpresys Lung®, Xpresys Lung 2®, and BDX-XL2) is a plasma-based proteomic screening test that measures 2 proteins (LG3BP and C163A) thought to be important in the development of lung cancer. The test considers their abundance along with five additional factors (age, nodule size, smoking status, edge, and location). It is intended for use after the diagnosis of a pulmonary nodule in patients whose risk category is indeterminate by current risk calculators and may help reclassify a nodule as lower risk (<5%) for malignancy (Biodesix, 2023).

Other proteomic tests include REVEAL Lung Nodule Characterization, which 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 a gene expression profiling test (Percepta) 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 three to five 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 methylation status of four genes that “display aberrant methylation in more than 50% of cancer samples and no aberrant methylation in normal tissue.” The authors confirm that their “methodological approaches, based on either ddMSP or NGS, exhibited an analytical sensitivity of 0.1% or lower, which is adequate to recognize the traces of nucleic acids originating from cancer cells.” When used on bronchial washings obtained from patients during fibre-optic bronchoscopy, the ddMSP demonstrated a 97% sensitivity 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. (2021) 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).

Li et al. (2013) first reported on the analytical validity of Nodify XL2. A 371-protein multiplexed multiple reaction monitoring (MRM) assay was developed to identify lung cancer biomarker candidates in blood samples. The authors initially determined that a total of 190 MRM assays were able to detect their target proteins in plasma, reflecting an overall success rate of 51%. This multiplexed MRM assay was then applied to 143 discovery samples and subsequently refined to a 13-protein classifier (Li et al., 2013).

### ***Clinical Utility and Validity***

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 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 of unnecessary invasive procedures (Lee et al., 2017).

The Percepta GSC was validated in a study by Mazzone et al. (2022). In patients with low and intermediate pre-test risk of cancer who were down-classified with Percepta GSC, the test demonstrated a > 99% and 91% NPV in these groups, respectively. The GSC may also up-classify cancer risk; patients with intermediate and high pre-test risk of cancer were up-classified with a 65.4% and 91.5% PPV, respectively. Sensitivity of the classifier was reported as 92.3% among patients with low and intermediate pre-test risk of cancer; however, this value increased to 95.5% when the classifier result was combined with data from bronchoscopy. The authors further concluded that if Percepta GSC were employed in the management of lung nodules, “50% of patients with benign lesions and 29% of patients with malignant lesions undergoing additional invasive procedures could have avoided these procedures” (Bhorade et al., 2019; Mazzone et al., 2022).

Li et al. (2013) established the performance of Nodify XL2 using a set of plasma samples. For this test, negative predictive value (NPV) is defined as the likelihood that a prediction of a benign tumor by the classifier is true. Specificity is defined as “the fraction of the benign nodules that the classifier is able to detect with high confidence.” With an assumed cancer prevalence of 15%, the classifier demonstrated a sensitivity of 82%, a specificity of 66%, and an NPV of 95% when run on an initial batch of “discovery” samples. In a follow up analysis on “validation” samples, the classifier demonstrated a sensitivity of 71%, a specificity of 44%, and an NPV of 90% (Li et al., 2013).

The prospective PANOPTIC Trial investigated the accuracy of Nodify XL2 and included a subgroup of 178 patients with a physician-assessed probability for malignancy (pCA)  $\leq 50\%$ . From this study, Silvestri et al. (2018) concluded that Nodify XL2 demonstrated a sensitivity of 97%, specificity of 44%, and an NPV of 98%, in its ability to distinguish benign and malignant nodules. The authors state that 40% fewer procedures would have been performed on benign nodules if the test were used to direct care. Notably however, use of the test would have misclassified 3% of malignant nodules, underscoring the importance of ensuring that all patients reclassified as low-risk using Nodify XL2 receive appropriate follow up care, to continually rule out malignancy (Silvestri et al., 2018).

Tanner et al. (2021) published a follow up to the PANOPTIC trial, observing patients for up to two years. In a cohort of 132 patients with nodules categorized as benign at year 1, all remained benign at year two. The authors conclude that the “performance characteristics [of the XL2 classifier] were maintained at year 2.” Nodify XL2 was also found to perform equally well in patients with solitary versus multiple nodules (Tanner et al., 2020). This is important because it is common for patients to present with more than one nodule. The authors further conclude that Nodify XL2 was shown to outperform the physician pCA, validated Mayo, Veterans Administration, and Brock models, based on area under curve (AUC) analysis (Tanner et al., 2021).

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 (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 et al., 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” (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 were 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).

There is a growing body of research investigating the utility of serum biomarker testing for the identification of lung cancer. However, the reported sensitivity of these panels is low and more work will likely be needed before they may be applied clinically. Doseeva et al. (2015) found that a panel of 3 tumor antigens (CEA, CA-125, and CYFRA 21–1) and 1 autoantibody marker (NY-ESO-1) discriminated between non-small cell lung cancer and controls with a sensitivity of 74%. P. J. Mazzone et al. (2018) further validated this panel, reporting a sensitivity and specificity of 49% and 96%, respectively. More recently, Fahrman et al. (2022) developed a blood-based biomarker panel for personalized lung cancer risk assessment called 4MP (four-marker protein panel), that consisted of the precursor form of surfactant protein B, CA-125, CEA, and cytokeratin-19 fragment. In combination with a lung cancer risk prediction model (PLCO<sub>m2012</sub>), the 4MP demonstrated a sensitivity of 88.4% and specificity of 56.2%, at a “≥ 1.0% 6-year risk threshold corresponding to the USPSTF 2021 criteria.”

## V. Guidelines and Recommendations

### American College of Chest Physicians (ACCP)

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. The guidelines state 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). The ACCP updated the guidelines for screening of lung cancer in 2021 but did not change the recommendations on the use of biomarkers in lung cancer screening (Mazzone et al., 2021). More generally however, the ACCP does acknowledge the importance that biomarkers will likely play in the evaluation of individuals with pulmonary nodules. They state that “research priorities include developing and validating risk assessment models to estimate the probability of cancer among individuals with small nodules or subsolid nodules, performing studies that compare the benefits and harms of alternative management strategies among individuals stratified by cancer risk, determining the safety of CT scan surveillance by examining outcomes among individuals who choose this strategy, and developing and validating novel noninvasive biomarkers to facilitate diagnosis and determine prognosis” (Gould et al., 2013).

### **National Comprehensive Cancer Network**

The NCCN guidelines for non-small cell lung cancer address the utility of molecular profiling after a cancer diagnosis has been made, “with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials” (NCCN, 2023b).

The NCCN Guidelines for small cell lung cancer state that molecular profiling can be considered in “rare cases for patients with extensive-stage small cell lung cancer disease who do not smoke tobacco, lightly smoke, or for pathologic dilemma” and should only be done “for patients who have never smoked tobacco with extensive-stage small cell lung cancer disease” (NCCN, 2022).

The NCCN Guidelines for lung cancer screening did not mention gene expression or molecular profiling as a potential diagnostic or screening tool (NCCN, 2023a).

### **European Society for Medical Oncology (ESMO)**

ESMO does not mention gene expression profiling in its guideline on the diagnosis, treatment and follow-up for early and locally advanced non-small cell lung cancer (Postmus et al., 2017).

The ESMO Guidelines for metastatic non-small cell lung cancer recommend 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). The guidelines also comment on the utility of blood monitoring for oncogenic driver mutations, noting that the ability to detect such alterations or other factors associated with disease resistance to treatment through blood sampling, improves disease monitoring (Planchard et al., 2018).

### **American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society (ATS/ERS/JRS/ALAT)**

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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 (Raghu et al., 2018).

A 2022 updated guideline was published that also includes recommendations for progressive pulmonary fibrosis (PPF). In a patient with interstitial lung disease of known or unknown etiology other than IPF, PPF was defined as a patient exhibiting 2 out of 3 of the following criteria occurring within the past year with no alternative explanation: worsening primary symptoms, physiological evidence of disease progression, and radiological evidence of disease progression. The committee made “no recommendation for or against the addition of [Envisia] genomic classifier testing for the purpose of diagnosing UIP in patients with ILD of undetermined type who are undergoing transbronchial forceps biopsy”, concluding that “research is also needed to improve the technique’s sensitivity, assess the downstream consequences of false-negative results (i.e., incorrectly categorizing a patient with the UIP pattern as not having the UIP pattern), and determine the ability of genomic classifier testing to differentiate UIP related to IPF and UIP related to other types of ILD” (Raghu et al., 2022).

#### **European Paediatric Soft Tissue Sarcoma Study Group**

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**

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).

## **VI. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

## VII. Applicable State and Federal Regulations

**DISCLAIMER:** If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

### Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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## IX. Policy History

Action Date	Action
06/01/2023	Initial policy implementation
11/21/2023	Policy approved by Medical Directors
12/15/2023	Policy approved at UMC
2/01/2025	Policy effective date following notification period