Molecular Testing in the Management of Pulmonary Nodules

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DESCRIPTION

Plasma based proteomic screening and gene expression profiling (GEP) 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 (CT)-guided biopsies, bronchoscopies or video assisted thoracoscopy are often required, but each carry procedure related complications ranging from post procedure pain to pneumothorax. Molecular diagnostic tests have been proposed to aid in risk-stratifying individuals to eliminate or necessitate the need for subsequent invasive diagnostic procedures.

Pulmonary nodules are common clinical problem that may be found as an incidental finding on a chest x-ray or computed tomography (CT) scan or during lung cancer screening studies of smokers. The primary question following detection of pulmonary nodules is the probability of malignancy, with subsequent management based on various factors such as the radiographic characteristics of the nodule(s) (e.g., size, shape, density) and individual factors (e.g., age, smoking history, previous cancer history, family history,

environmental/occupational exposures). The key challenge in the diagnostic workup for pulmonary nodules is appropriately ruling-in individuals for invasive diagnostic procedures and ruling-out individuals who should forego invasive diagnostic procedures. However, due to the low positive predictive value of pulmonary nodules detected radiographically, many unnecessary invasive diagnostic procedures and/or surgeries are performed to confirm or eliminate the diagnosis of lung cancer.

Plasma-Based Proteomic Screening for Pulmonary Nodules
Proteomics is the study of the structure and function of proteins. The study of the concentration, structure, and other characteristics of proteins in various bodily tissues, fluids and other materials has been proposed as a method of identifying and managing various diseases, including cancer. In proteomics, multiple test methods are used to study proteins. Immunoassays use antibodies to detect the concentration and/or structure of proteins. Mass spectrometry is an analytic technique that ionizes proteins into smaller fragments and determine mass and composition to identify and characterize them.

Plasma-based proteomic screening has been investigated to risk-stratify pulmonary nodules as likely benign to increase the number of individuals who undergo serial computed tomography (CT) scans of their nodules (active surveillance), instead of invasive procedures such as surgery or CT guided biopsy. Additionally, proteomic testing may also determine a likely malignancy in clinically low risk or intermediate risk pulmonary nodules, thereby permitting earlier detection in a subset of individuals.

Nodify XL2™ Test
Nodify XL2™ (Biodesix) is a plasma-based proteomic screening test that measures the relative abundance of proteins from multiple disease pathways associated with lung cancer using an analytic technique called multiple reaction monitoring mass spectroscopy. The role of the test is to aid physicians in differentiating likely benign from likely malignant nodules. If the test yields a likely benign result, individuals may choose active surveillance via serial CT scans to monitor the pulmonary nodule. If the test yields a likely malignant result, invasive diagnostic procedures would be indicated. The test is therefore only used in the management of pulmonary nodules to rule in or out invasive diagnostic procedures and does not diagnose lung cancer. Earlier generations of the test include Xpresys Lung and BDX-XL2 (Xpresys Lung 2). This current test combines measurements of two proteins with five clinical characteristics to assess the risk of malignancy. The Nodify XL2™ is intended for individuals with incidental lung nodules:

- $\geq$ 40 years
- 8-30 mm nodule
- $\leq$ 65% risk malignancy
- No previous diagnosis of cancer (individuals are eligible for Nodify XL2™ testing if history of non-lung cancer is > 5 years and risk of malignancy is $\leq$ 50%

REVEAL Lung Nodule Characterization
REVEAL Lung Nodule Characterization (MagArray) is a plasma-based protein biomarker test that may aid clinicians in characterizing indeterminate pulmonary nodules

(4-30 mm) in current smokers aged 25 years and older. The test uses immunoassay, microarray, and magnetic nanoparticle detection techniques. The REVEAL Lung Nodule Characterization score is presented on a scale from 0 to 100 with a single cut point at 50, and the score is calculated using an algorithm based on the measurement of 3 clinical factors (smoking history, individual age, nodule size) and 3 blood proteins (epidermal growth factor receptor [EGFR], prosurfactant protein B (ProSB), tissue inhibitor of metalloproteinases 1 (TIMP1) associated with the presence of lung cancer. This result may aid in the decision to perform a biopsy, or to consider routine monitoring.

EarlyCDT-Lung (Oncimmune, De Soto, KS) is a serum-based test that measures autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4, and SOX2) associated with small cell and non-small cell lung cancer (NSCLC). Unlike the Nodify XL2 (earlier generation tests Xpresys Lung, Xpresys Lung 2 [BDX-XL2]), the role of this test is to aid physicians in "ruling in" a diagnosis of malignancy.

Clinical Context and Test Purpose
The purpose of plasma-based proteomic screening in individuals with undiagnosed pulmonary nodule(s) is to stratify clinical risk for malignancy and eliminate or necessitate the need for invasive diagnostic procedures.

Patients
The relevant population of interest is individuals with undiagnosed pulmonary nodules. In particular, as outlined in the evidence based American College of Chest Physicians guidelines (2013) on the evaluation of individuals with pulmonary nodules, diagnosis and management of lung cancer, decision making about a single indeterminate lung nodule 8 to 30 mm in diameter on a computed tomography (CT) scan is complicated, requiring input about the individual's pretest probability of lung cancer, the characteristics of the lung nodule on CT, and shared decision making between the individual and physician about follow-up. Therefore, additional information in the segment of individuals with an indeterminate lung nodule, 8 to 30 mm in diameter would be particularly useful.

Interventions
The tests being considered is plasma-based proteomic screening Nodify XL2 (earlier generations Xpresys Lung, Xpresys Lung test 2 [BDX-XL2]), EarlyCDT® Lung and REVEAL Lung Nodule Characterization.

Comparators
The following practice is currently being used: standard clinical management using clinical and radiographic risk factors.

Outcomes
The potential beneficial outcomes of primary interest are avoiding an unneeded invasive biopsy of a nodule that would be negative for lung cancer or initiating biopsy for a nodule that would otherwise have been followed with serial CTs.

Potential harmful outcomes are those result from false-positive or false-negative results. False-positive test results can lead to unnecessary invasive diagnostic procedures, and procedure related complications. False-negative test result can lead to lack of pulmonary nodule surveillance or lack of appropriate invasive diagnostic procedures to diagnosis malignancy.

Review of Evidence
(Reviewed June 10, 2022) Hayes a Smplry company completed a molecular test assessment which reviewed Nodify XL2 liquid biopsy test to assist identifying low to moderate risk individuals with likely benign incidental lung nodules which reported lacking evidence to use the Nodify XL2 in the identified individual subset. Additional studies are needed to support pysican clinical decision making to improve net health outcomes. (*Accessed July 2022*)

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Several studies were identified that reported on the development and validation of plasma-based classifier test to predict malignancy (Xpresys Lung and Xpresys Lung 2 (BDX-XL2]).

(2018) Silvestri et. al reported on the validation of the Xpresys Lung test 2 (BDX-XL2) in a prospective, multicenter observational study (Pulmonary Nodule Plasma Proteomic Classifier Study [PANOPTIC]) with retrospective evaluation of 685 patients with 8 to 30 mm lung nodules and a low pretest probability of malignancy ≤ 50%. Out of the 685 patients a total of 293 were excluded (failed include/exclusion criteria, no blood sample, no baseline CT scan, incomplete clinical data, sample inadequate for protein analysis, protocol deviations), yielding 392 eligible for analysis. This study integrated classifier's performance focused on the subgroup of 178 patients having a lung nodule with pCA ≤ 50%. Of these, 66 were classified as likely benign, 65 of which had a benign nodule, while 1 of 29 malignant nodules (3%) was misclassified as likely benign. Of the 149 benign nodules in the study, 44% were correctly classified as likely benign. For the 71 patients who had invasive procedures, 42 had benign nodules. The authors concluded; this study is the first we are aware of to assess the accuracy of an integrated plasma proteomics classifier in patients with pulmonary nodules in a geographically diverse population with varying risk of cancer. In those with low to moderate risk nodules (pCA ≤ 50%), a "likely benign" test result could safely allow patients to be followed up by using serial imaging. Further research is needed to assess the effect of incorporating this test into diagnostics algorithm for nodule management in the hope of reducing unnecessary procedures in patients without cancer.

(2017) Kearney et. al conducted a prospective, multicenter, observational trial with retrospective evaluation of the performance of molecular and clinical makers (Xpresys Lung). Patients with indeterminate pulmonary nodule were enrolled at 12 geographically

diverse sites in the U.S. Of these sites seven were academic sites and five were community sites. Eligible patients were those with a lung nodule of size 8-20 mm, minimum 40 years of age, who had recently completed a CT guided needle aspiration or bronchoscopic biopsy with an established diagnosis or scheduled for a surgical biopsy. The assay Xpresys Lung is based on mass spectroscopy (MRM-MS), clinical factors collected included age, smoking status, nodule diameter, nodule speculation and nodule location. All samples were analyzed using the Xpresys Lung assay. A total of 475 subjects were enrolled prospectively from April 2012 to December 2014 in the registered study NCT01752101. Of these, 50 subjects violated the inclusion/exclusion criteria: 43 additional subjects violated the blood sample collection protocol. Of the remaining 353 patients, 222 had nodule size 8-20 mm. In this population of subjects, the cancer prevalence was 81% (180 out of 222 subjects). The authors concluded, the integration of molecular markers with clinical risk factors can increase classification performance over molecular markers (clinical factors) on their own. However, this requires further validation and investigation on lung nodule population.

(2015) Vachani et. al reported on a retrospective, multicenter, case-control study on the validation for classifier comprising five diagnostic and six normalization proteins designed to identify likely benign lung nodules in a sample of 141 plasma samples associated with indeterminate pulmonary nodules 80 to 30 mm in diameter. The classifier achieved validation on 141 lung nodule-associated plasma samples based on predefined statistical goals to optimize sensitivity. Using a population based non-small-cell lung cancer prevalence estimate of 23% for 8 to 30 mm indeterminate pulmonary nodules (IPNs), the classifier identified likely benign lung nodules with 90% negative predictive value and 26% positive predictive value, at 92% sensitivity and 20% specificity, with the lower bound of the classifier's performance at 70% sensitivity and 48% specificity. Classifier scores for the overall cohort were statistically independent of patient age, tobacco use, nodule size, and chronic obstructive pulmonary disease diagnosis. The classifier also demonstrated incremental diagnostic performance in combination with a four-parameter clinical model. Limitations of this study derive from specifics of the experimental design relating to the classifier performance priorities and molecular biomarkers and the use of archival samples from academic centers, though representative of the target population, may raise questions about the classifier’s prospective performance in the general population. Future evaluations of the proteomic expression classifier in prospective lung nodule studies may clarify some of the performance issues.

(2013) Li et. al reported on the development and validation of the 13 protein plasma test, or classifier, proposed to differentiate benign from malignant pulmonary lung nodules. They used multiple reaction monitoring (MRM) mass spectrometry (MS) to measure the concentrations of candidate proteins in plasma. The test identifies classifier proteins likely modulated by a few transcription regulators (NF2L2, AHR, MYC, and FOS) associated with lung cancer and inflammation. The MRM assays were applied in a three-site discovery study (n = 143) on plasma samples from patients with benign and Stage IA cancer matched on nodule size, age, gender and clinical site, producing a 13-protein classifier. The classifier was validated on an independent set of plasma samples (n =

104), exhibiting a high negative predictive value (NPV) of 90%. Validation performance on samples from a non-discovery clinical site showed NPV of 94%, The main limitation of this study is that both discovery and validation studies were conducted using retrospective samples. A prospective study on intended use samples is required to further validate the utility of the classifier for clinical use.

(2012) Pecot et. al validated a 7-peak matrix-assisted laser desorption ionization mass spectrometry (MALDI MS) proteomic signature in 2 prospective cohorts of patients with one or more pulmonary nodules on chest computed tomography (CT) (N=379). The first, cohort A, combined patients from Vanderbilt University and the Veterans Affairs Medical Center, Nashville, TN and the second cohort B, included patients from Mayo Clinic, Rochester, MN. The average computed tomography (CT) measured nodule size in cohorts A and B was 37.83 versus 23.15 mm among patients with lung cancer and 15.82 versus 17.18 mm among those without, respectively. In cohort A, the area under the curve (AUC) increased from 0.68 to 0.86 after adding chest CT imaging variables to the clinical results, but the proteomic signature did not provide meaningful added value. In contrast, in cohort B, the AUC improved from 0.46 with clinical data alone to 0.61 when combined with chest CT imaging data and to 0.69 after adding the proteomic signature (IDI of 20% P = 0.0003). In addition, in a subgroup of 100 nodules between 5 and 20 mm in diameter, the proteomic signature added value with an IDI of 15% ($P \leq 0.0001$). The authors concluded the results show that this serum proteomic biomarker signature may add value to the clinical and chest CT evaluation of indeterminate lung nodules. Further prospective validation among a larger cohort of patients presenting with indeterminate pulmonary nodules in the context of a screening strategy is needed.

Section Summary
Clinical validation studies were identified for two versions of a proteomic classifier (Xpresys Lung and Xpresys Lung test 2 [BDX-XL2]. 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 Xpresys Lung test 2 [BDX-XL2]. One validation study on the version two has been identified. The classifier has been designed to have high pretest probability ($\leq$ 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 as priori. Validation in an independent sample in the intended use population is needed. In general, the Xpresys Lung classifier has been designed to have a high NPV (negative predictive value). However, its clinical validity is uncertain given that studies have reported on slightly different versions of the test. Also, studies have not reported how it reclassifies patients relative to clinical classifiers regarding risk.

Note: *Nodify XL2 (Integrated Diagnostics [Indi], purchased by Biodesix) and the earlier generation test is Xpresys Lung test 2 [BDX-XL2]).*

The following validation study was identified for the REVEAL Lung Nodule Characterization.

(2019) Arfoosh et. al assessed the results of a novel, plasma-based multiplexed protein assay (REVEAL Lung Nodule Characterization) in a clinical experience program. Fifty-four consecutive plasma samples were evaluated, and all samples were from patients who are current smokers, aged 25 years and older, and have an indeterminate pulmonary nodule 0.4 to 3 cm in diameter. The mean patient age was 65.5 years, and the mean nodule size was 1.0 cm. Twenty-six patients were male (52% female). Of the 54 tests, the assay results for 23 individuals were determined to be in the lower risk of malignancy range (score < 49). Forty-two patients had a pre-test probability in the intermediate risk range as calculated by the VA Clinical Model. Of those patients, the assay characterized 22 as having a lower risk of malignancy (52%). The authors concluded, the novel, multiplexed, plasma protein assay can be used as a non-invasive risk assessment tool by clinicians in characterizing indeterminate pulmonary nodules. When the results of this assay are combined with the traditional clinical risk factors (i.e. patient history), risk stratification for indeterminate pulmonary nodules may be improved compared to current methods in clinical practice. We hypothesize the assay will significantly reduce costs to the healthcare system while further improving a patient's quality of care. Providers and their patients may consider using this novel assay prior to proceeding with an invasive evaluation of their patient's indeterminate nodule. Although the blood-based biomarker assay has shown promising results in differentiating malignant from benign lesions, further research is needed to more broadly assess the impact of the test on clinical decision making. Ideally, long-term follow-up including the rate of lung cancer deaths prevented using this test is desired to further verify this as an effective risk assessment of lung cancer.

(2018) Trivedi et. al validated a plasma-based multiplexed assay for classifying indeterminate pulmonary nodules (IPN) by discriminating between those with a lung cancer diagnosis established pathologically and those found to be clinically and radiographically stable for at least one year. Using a novel technology (REVEAL Lung Nodule Characterization) they developed assays for plasma proteins associated with lung cancer into a panel for characterizing the risk that an IPN found on chest imaging is malignant. The assay panel was evaluated with a cohort of 277 samples, all from current smokers with an IPN 4-30 mm. Subjects were divided into training and test sets to identify a Support Vector Machine (SVM) model for risk classification containing those proteins and clinical factors that added discriminatory information to the Veteran's Affairs (VA) Clinical Factors Model. The algorithm was then evaluated in an independent validation cohort. Among the 97 validation study subjects, 68 were grouped as having intermediate risk by the VA model of which the SVM model correctly identified 44 (65%) of these intermediate-risk samples as low (n=16) or high risk (n=28). The SVM model negative predictive value (NPV) was 94% and its sensitivity was 94%. The authors concluded, risk stratification for benign nodules is improved with the SVM model compared to current clinical practice methods. We hypothesize that patients with benign disease may benefit the most from this rule-out assay by avoiding unnecessary

lung biopsy and subsequent overtreatment, while improving the quality of care and reducing the risk of harm from these procedures. This study had several limitations, including the need to fully assess the test in other races, and how other conditions (such as obesity and its pro-inflammatory state, or steroid use) may affect the assay performance. This algorithm is also dependent on a compliant patient; those who do not adhere to follow-up appointments may have their cancer diagnosis missed. A clinical utility study to assess the impact of the algorithm on clinical decision making is also needed as outlined in the American Thoracic Society policy statement. Ideally, long-term follow-up including the rate of lung cancer deaths prevented using this test is desired to verify this as an effective marker of aggressive lung cancer.

Section Summary
While the REVEAL biomarker assay has shown promising results in differentiating malignant from benign lesions, further research is needed to more broadly assess the impact of the test on clinical decision making. Ideally long-term follow-up including the rate of lung cancer deaths prevented using this test is desired to further verify this an effective risk assessment of lung cancer. This plasma-protein signature should also be more directly assessed in all races, as well as specific conditions such as obesity and its pro-inflammatory state, steroid use, etc., that may affect the test performance. Further clinical studies are warranted to further define the value of the test in accurately identifying individuals who are most likely to benefit from serial surveillance or early treatment, while reducing the rate of false-positive results, unnecessary interventions, and their associated morbidity and healthcare costs.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary therapy.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with or without the test. The preferred evidence would be from randomized controlled trials. No evidence directly demonstrating improved outcomes in individuals managed with Xpresys Lung test 2 [BDX-XL2] was identified.

(2019) Smester et. al in a case report, reported on the clinical work-up of a high-risk patient with an indeterminate pulmonary nodule. In this clinical case, the assay (REVEAL Lung Nodule Characterization) provided important, additional information that modified the patient's management. Although the patient was an anxious current smoker, and had a 7 mm nodule, the multiplexed plasma protein assay test score of 34 (out of 100) indicated lower risk that the nodule was malignant. This finding helped the patient and physician make a better-informed decision to adopt a serial surveillance approach. The authors concluded, we reported on a patient case illustrating the benefit of novel, lung cancer-specific biomarker assay. The assay can be used as a non-invasive risk assessment tool for clinicians in characterizing indeterminate pulmonary nodules. When

the results of the assay are combined with the traditional risk factors, risk stratification for indeterminate pulmonary nodules is improved compared to current methods in clinical practice. We hypothesize the assay will significantly reduce costs to the healthcare system while further improving a patient's quality of care. Providers and their patients may consider using this novel assay prior to proceeding with an invasive evaluation of their patient's indeterminate pulmonary nodule. Although the REVEAL biomarker assay has shown promising results in differentiating malignant from benign lesions, further research is needed to more broadly assess the impact of the test on clinical decision making. Ideally long-term follow-up including the rate of lung cancer deaths prevented using this test is desired to further verify this an effective risk assessment of lung cancer.

(2015) Vachani et. al reported on a multicenter prospective-retrospective study of patients with indeterminate pulmonary nodules. A plasma protein classifier (Xpresys Lung) was used on 475 patients with nodules 8 to 30 mm in diameter who had an invasive procedure to confirm the diagnosis. Using the classifier, 32.0% (95% CI, 19.5% to 46.7%) of surgeries and 31.8% (95% CI, 20.9% to 44.4%) of invasive procedures (biopsy and/or surgery) on benign nodules could have been avoided, while 24.0% (95% CI, 19.2% to 29.4%) of patients with malignancy would have been triaged to CT surveillance. By comparison, 24.5% (95% CI, 16.2% to 34.4%) of patients with malignancy were routed to CT surveillance using clinical parameters alone.

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

- Changes in Management
    - The clinical setting in which a proteomic classifier with high NPV is used, are individuals with undiagnosed pulmonary nodules detected by CT.
    - Indirect evidence regarding Xpresys Lung test 2 [BDX-XL2] suggests that 36% of invasive procedures (biopsy and/or surgery) on benign nodules could have been avoided, if the test is used in patients with a low to moderate ($\leq$ 50%) pretest probability of malignancy. Three percent of malignant lesions may be missed, although these patients would be followed by CT to verify lack of progression.
- Improved Outcomes
    - Indirect evidence suggests that use of proteomic classifier with a high NPV has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. Compared with the standard of care plan, some patients without cancer will have avoided an unnecessary invasive procedure, which is weighed against the increase in missed cancers in patients who had lung cancer but tested as negative on the proteomic classifier with a high NPV test.
    - Whether the tradeoff between avoiding unneeded surgeries and the potential for missed cancer is worthwhile depends, in part, on patient and physician preferences. Missed malignancies would likely be continued to be followed by active surveillance using low-dose CT imaging. In the context of lung

cancers, overall survival (OS) depends on the detection of lung cancer at early, more treatable stages.

- Avoiding invasive procedures in situations where patients are at very low likelihood of having lung cancer is likely beneficial, given the known complications of invasive procedures (e.g. pneumothorax). However, reduction in unnecessary invasive procedures must be weighed against outcomes and harms associated with a missed diagnosis of lung cancer at earlier, more treatable stages.

Section Summary
Indirect evidence suggests that a proteomic classifier with high NPV has the potential to reduce the number of invasive procedures to definitively diagnose benign disease versus malignancy. While these results are promising further clinical studies are warranted to more broadly assess the impact of these tests on clinical decision making, by accurately identifying individuals who are most likely to benefit from serial surveillance or early treatment, while reducing the rate of false-positive results, and unnecessary interventions, Also, long-term follow-up is needed to include the rate of lung cancer deaths prevented using this test to further verify this an effective risk assessment of lung cancer.

EarlyCDT® Lung Test
This test, while extensively validated in newly diagnosed lung cancer and nodule cohorts, has not been evaluated extensively as a part of traditional low-dose CT based screening program.

(2021) González Maldonado examined the diagnostic accuracy of the EarlyCDT® test in 46 individuals with lung cancer detected by low dose computed tomography (CT). The EarlyCDT® lung test produced positive ("high level") results in 6 of the 46 individuals, for a sensitivity of 13.0% (95% confidence interval [CI], 4.9 to 26.3%). In the individuals with lung nodules < 10 mm in diameter, "high level" results were obtained in 1 out of 11 cases (sensitivity: 9.1%, 95% CI, 0.23 to 41.3%). For the remaining individuals with lung nodules ≥ 10 mm, the estimated sensitivity was 14.7% (95% CI, 4.9 to 31.3%) (number of 'high level' results were not reported for the latter group). The investigators also tested 90 individuals randomly selected from all cancer-free individuals (baseline controls) and 90 individuals randomly selected from among cancer-free individuals with suspicious nodules on CT scans (suspicious nodule controls). They found that the EarlyCDT® test had a specificity of 88.9% (95% CI, 80.5 to 94.5%) in the baseline control group and 91.1% (95% CI, 83.2 to 96.1%) in the suspicious nodule control group.

(2021) Sullivan et. al reported on results of a phase IV biomarker evaluation of whether using the EarlyCDT® Lung test and any subsequent computed tomography (CT) scanning to identify those at high risk of lung cancer reduces the incidence of individuals with stage III/IV/unspecified lung cancer at diagnosis compared with the standard clinical practice at the time the study began. The Early Diagnosis of Lung Cancer Scotland (ECLS) trial was a randomized controlled trial of 12,208 participants at risk of developing lung cancer in Scotland in the UK. The intervention arm received the

EarlyCDT®-Lung test and, if test-positive, low-dose CT scanning 6-monthly for up to 2 years. EarlyCDT®-Lung test-negative and control arm participants received standard clinical care. Outcomes were assessed at 2 years post-randomization using validated data on cancer occurrence, cancer staging, mortality and comorbidities. At 2 years, 127 lung cancers were detected in the study population (1.0%). In the intervention arm, 33 out of 56 (58.9%) lung cancers were diagnosed at stage III/IV compared with 52 out of 71 (73.2%) in the control arm. The hazard ratio for stage III/IV presentation was 0.64 (95% CI 0.41–0.99). There were nonsignificant differences in lung cancer and all-cause mortality after 2 years. ECLS compared EarlyCDT®-Lung plus CT screening to standard clinical care (symptomatic presentation) and was not designed to assess the incremental contribution of the EarlyCDT®-Lung test. The observation of a stage shift towards earlier-stage lung cancer diagnosis merits further investigations to evaluate whether the EarlyCDT®-Lung test adds anything to the emerging standard of low-dose CT (LDCT). In conclusion, ECLS demonstrates that blood-based biomarker panels, such as the EarlyCDT®-Lung test, followed by Low Dose CT can detect stage I/II lung cancer. Follow-up analyses will be performed after 5 and 10 years, although we recognize that the absolute lung cancer incidence would be higher than that detected due to deaths from other causes. Further investigation in large, community-based studies will be required to determine the long-term impact of performing the EarlyCDT®-Lung test with LDCT on mortality, cost-effectiveness, the level of risk that should be targeted, the time interval between tests and how to improve the engagement of people at the highest risk

Section Summary: EarlyCDT Lung Test
EarlyCDT®-Lung (OncImmune), is a 7-autoantibody panel, consisting of p53, CAGE, NY-ESO-1, SOX2, GBU4–5, HuD, and MAGE-A4. While study results may be promising especially in stage I/II lung cancer further investigation is needed to determine the long-term impact of performing the EarlyCDT®-Lung test with LDCT on mortality, cost-effectiveness, the level of risk that should be targeted, the time interval between tests and how to improve the engagement of people at the highest risk.

Gene Expression Profiling
Gene expression profiling (GEP) is the measurement of the activity of genes within cells. Messenger RNA serves at the bridge between DNA and functional proteins. Multiple molecular techniques such as Northern blots, ribonuclease protection assay, in situ hybridization, spotted complementary DNA arrays, oligonucleotide arrays, reverse transcriptase polymerase chain reaction, and transcriptome sequencing are used in gene expression profiling (GEP). An important role of gene expression profiling (GEP) in molecular diagnostics is to detect cancer associated gene expression of clinical samples to assess for the risk of malignancy.

Gene Expression Profiling for an Indeterminate Bronchoscopy Result
The Percepta® Bronchial Genomic Classifier (Veracyte) is a 23 gene, gene expression profiling test that analyzes genomic changes in the airways of current of former smokers to assess an individual's risk of having lung cancer, without the direct testing of a pulmonary nodule. The test is indicated for current and former smokers following an

indeterminate bronchoscopy result to determine the subsequent management of pulmonary nodules (e.g., active surveillance or invasive diagnostic procedures) and does not diagnose lung cancer.

Clinical Context and Test Purpose
The purpose of gene expression profiling of bronchial brushings in individuals who undergo bronchoscopy for the diagnosis of suspected lung cancer but who have an indeterminate cytology result is to stratify the clinical risk for malignancy and eliminate the need for invasive diagnostic procedures.

Patients
The relevant population of interest, according to the manufacturer, is individuals with physician-assessed low or intermediate pretest risk of malignancy who are current or former smokers with inconclusive bronchoscopy for suspected lung cancer.

Interventions
The test being considered is gene expression profiling (GEP) of bronchial brushings to include Percepta® Bronchial Genomic Classifier (Veracyte).

Comparators
The following practice is currently being used: standard clinical management without gene expression profiling (GEP). The management of individuals with suspected lung cancer who have an indeterminate bronchoscopy result is not entirely standardized. However, it is likely that in standard practice many individuals would have a surgical biopsy, transthoracic needle aspiration, or another test, depending on the location of the nodule. According to the guidelines from the American College of Chest Physicians (2013) for establishing the diagnosis of lung cancer, in individuals suspected of having lung cancer, who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. If the bronchoscopy results are nondiagnostic and suspicion of lung cancer remains, additional testing is recommended (Grade 1B recommendation).

Outcomes
The potential beneficial outcomes of primary interest are avoiding an unneeded invasive biopsy of a nodule that would be negative for lung cancer.

Potential harmful outcomes are those result from false-positive or false-negative results. False-positive test results can lead to unnecessary invasive diagnostic procedures, and procedure related complications. False-negative test result can lead to lack of pulmonary nodule surveillance or lack of appropriate invasive diagnostic procedures to diagnosis malignancy.

Review of Evidence
(Reviewed March 2022) Hayes a Smplr company completed a Molecular Test Assessment in 2020 reporting the Percepta Genomic Sequencing Classifier (GSC) test utilized on on individuals who are current or former smokers with indeterminate

bronchoscopy result the evidence is not sufficient to support the use of the Percepta (GSC) test. Additional studies reporting and reviewing the clinical validity, and utility are needed. (*Accessed July 2022*)

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

(2015) Whitney et. al reported on the development and initial validation of an RNA based gene expression classifier from airway epithelial cells designed to be predictive of cancer in current and former smokers undergoing bronchoscopy for suspected lung cancer. Samples were from patients in the Airway Epithelium Gene Expression in the Diagnosis of Lung Cancer (AEGIS) trials, which were 2 prospective observational, cohort studies (AEGIS-1, AEGIS-2), for current or former smokers undergoing bronchoscopy for suspected lung cancer.

Cohort details are described in Silvestri et. al (2015) below. A total of 299 samples from AEGIS-1 (223 cancer positive and 76 cancer free subjects) were used to derive the classifier. Data from 123 patients in a prior study with a non-diagnostic bronchoscopy were used as an independent test set. In the final model, the classifier included 17 genes, patient age, and gene expression correlates and was reported as a dichotomous score ($\geq$ 0.65 as cancer positive, < 0.65 as cancer negative). This classifier had a receiver operating characteristic (ROC) curve AUC (area under the curve) of 0.78 (95% CI, 0.70-0.86) in patients whose bronchoscopy did not lead to a diagnosis of lung cancer (n = 134). In the validation cohort, the classifier had a similar AUC of 0.81 (95% CI, 0.73-0.88) in this same subgroup (n = 118). The classifier performed similarly across a range of mass sizes, cancer histologies and stages. The negative predictive value was 94% (95% CI, 83-99%) in subjects with a non-diagnostic bronchoscopy.

(2015) Silvestri et. al reported on the diagnostic performance of the gene expression classifier developed in Whitney et. al (2015), in a sample size of 639 patients enrolled in 2 multicenter prospective studies (AEGIS-1, n=298 patients; AEGIS-2 n=341 patients). The study enrolled patients who were undergoing clinically indicated bronchoscopy for a diagnosis of possible lung cancer and had a history of smoking. Before the bronchoscopy, the treating physician assessed each patients' probability of having cancer with a 5-level scale (<10%, 10.-39%, 40.60%, 61.85%, >85%). Patients were followed until a diagnosis was established (either at the time of bronchoscopy or subsequently by another biopsy means) or until 12 months after bronchoscopy. Of the 639 patients in the validation study who underwent bronchoscopy. A total of 43% of bronchoscopic examinations were nondiagnostic for lung cancer, and invasive procedures were performed after bronchoscopy in 35% of patients with benign lesions. In AEGIS-1, the classifier had an area under the receiver-operating-characteristic curve (AUC) of 0.78 (95% confidence interval [CI], 0.73 to 0.83), a sensitivity of 88% (95% CI, 83 to 92), and a specificity of 47% (95% CI, 37 to 58). In AEGIS-2, the classifier had an AUC of 0.74 (95% CI, 0.68 to 0.80), a sensitivity of 89% (95% CI, 84 to 92), and a specificity of 47% (95% CI, 36 to

59). The combination of the classifier plus bronchoscopy had a sensitivity of 96% (95% CI, 93 to 98) in AEGIS-1 and 98% (95% CI, 96 to 99) in AEGIS-2, independent of lesion size and location. In 101 patients with an intermediate pretest probability of cancer, the negative predictive value of the classifier was 91% (95% CI, 75 to 98) among patients with a nondiagnostic bronchoscopic examination. The classifier improved prediction of cancer compared with bronchoscopy alone, but comparisons with a clinical predictor were not reported. For the subset of patients with a nondiagnostic bronchoscopy, the classifier performance was presented by the pretest physician-predicted risk if cancer. For most subpopulations, there was a very high NPV. However, there were 13 false negatives, 10 of which were considered at high (>60%) risk of cancer pre-bronchoscopy.

Section Summary: Gene Expression Profiling for an Indeterminate Bronchoscopy Result

Two multicenter prospective studies have provided evidence of the clinical validity of a bronchial genomic classifier in current or former smokers undergoing bronchoscopy for suspicion of lung cancer. For individuals with intermediate risk of lung cancer with nondiagnostic bronchoscopic examination, the NPV was 91%. However, there has been limited replication outside of a single trial group.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. The preferred evidence would be from randomized controlled trials.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

(2021) Lee et al. reported on an analysis of data from a prospective registry study of individuals with pulmonary nodules who had a nondiagnostic bronchoscopy. A total of 283 individuals in the registry had a Percepta test, with at least 1 year of follow-up after testing. Of these, 213 (75.3%) were assessed by physicians prior to bronchoscopy as having either had a low (n=39) or intermediate (n=174) risk of malignancy. The primary endpoint of the analysis was to measure down-classification using Percepta test results in this low- and intermediate-risk group. Invasive procedures were initially planned in 67 of the 213 individuals (31%). After consideration of Percepta results, 23 of the 67 (34%) were down classified and 17 individuals underwent surveillance instead of invasive procedures. The reduction in recommendations for invasive procedure recommendations with Percepta test results was statistically significant, $p<0.01$. At the 1-year follow-up, 14

of the 23 individuals (61%) continued to undergo surveillance. The remaining 70 of 283 individuals (24.7%) had a high pretest risk of malignancy. The secondary endpoint of the analysis was to evaluate up-classification based on Percepta results. A total of 60 of 70 individuals (85.7%) were up classified based on Percepta results to very high risk. Forty high-risk individuals were diagnosed with malignancy, including 37 (92 %) of those who had been up classified and 3 for whom recommendations were unchanged. There was not a statistically significantly longer time to diagnosis in the individuals with unchanged recommendations; however, the numbers of individuals are small. The study was not randomized and did not compare health outcomes in individuals managed with and without the Percepta test.

(2016) Ferguson et. al conducted a randomized, prospective, decision impact survey study assessing pulmonologist recommendations in patients undergoing workup for lung cancer who had an inconclusive bronchoscopy. Cases with an intermediate pretest risk for lung cancer were selected from the AEGIS trials and presented in a randomized fashion to the pulmonologists either with or without the patient's bronchial genomic classifier result to determine how the classifier results impacted physician decisions. Two hundred two physicians provided 1523 case evaluations on 36 patients. Invasive procedure recommendations were reduced from 57% without the classifier result to 18% with a negative (low risk) classifier result ($p < 0.001$). Invasive procedure recommendations increased from 50 to 65% with a positive (intermediate risk) classifier result ($p < 0.001$). When stratifying by ultimate disease diagnosis, there was an overall reduction in invasive procedure recommendations in patients with benign disease when classifier results were reported (54 to 41 %, $p < 0.001$). For patients ultimately diagnosed with malignant disease, there was an overall increase in invasive procedure recommendations when the classifier results were reported (50 to 64 %, $p = 0.003$). Limitations of this study include: the physicians were provided a summary of the patient's clinical presentation (age, gender, comorbidities), smoking history (pack years, years since quitting) and exposure history, physical exam findings, lesion details from CT and PET reports (nodule diameter, location, presence of adenopathy), but did not have direct access to the imaging which can impact decision making in this setting; physicians who chose PET as the management option were notified that the PET results were indeterminate, prompting them to make another management choice; this was a clinical decision impact study presented in survey form and not a clinical trial or registry, as such it can only approximate clinical utility using responses from a population who may have some form of selection bias for entering this type of study and decisions made in the survey may not accurately reflect those made at point of care; and clinical decision making is ultimately modulated by patient preferences which was not captured by this survey. The authors concluded that the findings suggest that a negative (low risk) bronchial genomic classifier result reduces invasive procedure recommendations following an inconclusive bronchoscopy and that the classifier overall reduces invasive procedure recommendations among patients ultimately diagnosed with benign disease. These 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.

(2016) Vachani et. al reported on rates of invasive procedures from AEGIS 1 and 2. Of 222 patients, 188 (85%) had an inconclusive bronchoscopy and follow-up procedure data available for analysis. Seventy-seven (41%) patients underwent an additional 99 invasive procedures, which included surgical lung biopsy in 40 (52%) patients. Benign and malignant diseases were ultimately diagnosed in 62 (81%) and 15 (19%) patients, respectively. Among those undergoing surgical biopsy, 20 (50%) were performed in patients with benign disease. If the classifier had been used to guide decision making, procedures could have been avoided in 21 (50%) of 42 patients who had additional invasive testing. Further, among 35 patients with an inconclusive index bronchoscopy who were diagnosed with lung cancer, the sensitivity of the classifier was 89%, with 4 (11%) patients having a false-negative classifier result. Invasive procedures after an inconclusive bronchoscopy occur frequently, and most are performed in patients ultimately diagnosed with benign disease.

Section Summary: Gene Expression Profiling for an Indeterminate Bronchoscopy Result

Direct evidence of the clinical utility for gene expression profiling of bronchial brushings is lacking. Indirect evidence suggests that Percepta® Bronchial Genomic Classifier has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. However, long-term follow-up data would be required to determine the survival outcomes in individuals with a missed diagnosis of lung cancer at earlier, more treatable stages.

Summary of Evidence

For individuals with undiagnosed pulmonary nodules detected imaging, who receive plasma-based proteomic screening, the evidence includes a prospective cohort and prospective-retrospective studies. Clinical validation studies were identified for two versions of a proteomic classifier Xpresys Lung and Xpresys Lung test 2 [BDX-XL2]. 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 (Xpresys Lung test 2 [BDX-XL2]). 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 individuals with low to moderate pretest probability ($\leq$ 50%) of a malignant pulmonary nodule. The primary limitation of this study is that a high number of individuals 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 net health outcomes.

For individuals with indeterminate pulmonary nodules (4-30 mm) by imaging, who receive plasma-based proteomic screening using the REVEAL Lung Nodule Characterization test, the evidence includes retrospective validation studies and case

reports. While the REVEAL biomarker assay has shown promising results in differentiating malignant from benign lesions, further research is needed to more broadly assess the impact of the test on clinical decision making. Ideally long-term follow-up including the rate of lung cancer deaths prevented using this test is desired to further verify this an effective risk assessment of lung cancer. This plasma-protein signature should also be more directly assessed in all races, as well as specific conditions such as obesity and its pro-inflammatory state, steroid use, etc., that may affect the test performance. Further clinical studies are warranted to further define the value of the test in accurately identifying individuals who are most likely to benefit from serial surveillance or early treatment, while reducing the rate of false-positive results, unnecessary interventions, and their associated morbidity and healthcare costs. The evidence is insufficient to determine the effects of the technology on net health outcomes.

For individuals with indeterminate pulmonary nodules who received the EarlyCDT-Lung test, while study results may be promising from 2021 Sullivan et. al. that reported on phase IV biomarker evaluation of whether using the EarlyCDT Lung test and any subsequent imaging scanning to identify those at high risk of lung cancer reduces the incidence of individuals with stage III/IV/unspecified lung cancer at diagnosis compared with the standard clinical practice, further investigation is needed to determine the long-term impact of performing the EarlyCDT-Lung test with LDCT on mortality, cost-effectiveness, the level of risk that should be targeted, the time interval between tests and how to improve the engagement of people at the highest risk. The evidence is insufficient to determine the effects of the technology on net health outcomes.

For individuals with undiagnosed pulmonary nodules following indeterminate bronchoscopy results for suspected lung cancer who receive gene expression profiling of bronchial brushings, the evidence includes multicenter prospective studies. Direct evidence of the clinical utility for gene expression profiling of bronchial brushings is lacking. Indirect evidence suggests that Percepta® Bronchial Genomic Classifier has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. However, long-term follow-up data would be required to determine the survival outcomes in individuals with a missed diagnosis of lung cancer at earlier, more treatable stages. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American Thoracic Society (ATS)
(2017) The American Thoracic Society published a position statement on the evaluation of molecular biomarkers for the early detection of lung cancer. The goal was to develop a policy statement that provides guidance about the level of evidence required to determine that a molecular biomarker, used to support early lung cancer detection, is appropriate for clinical use. Key points made in the statement include the following:

- 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 biomarker used to assist with lung nodule management 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.

The society concluded the application of molecular biomarkers to assist with the early detection of lung cancer has the potential to substantially improve our ability to select patients for lung cancer screening, and to assist with the characterization of indeterminate lung nodules. To support the application of molecular biomarkers in these clinical settings there must be evidence that the molecular biomarker leads to clinical decisions whose benefits outweigh their harms. Although it is tempting to apply novel testing based on promising discovery or validation level studies, the lung cancer community should insist on additional evidence of clinical utility before changing practice.

National Comprehensive Cancer Network (NCCN)

- **Lung Cancer Screening 2.2022**
    - Did not mention plasma-based proteomic screening testing or gene expression profiling as a potential diagnostic or screening tool.
- **Non-Small Cell Lung Cancer Version 3.2022**
    - Did not mention plasma-based proteomic screening testing or gene expression profiling as a potential diagnostic or screening tool.
- **Small Cell Lung Cancer Version 2.2022**
    - Did not mention plasma-based proteomic screening testing or gene expression profiling as a potential diagnostic or screening tool.

(*Accessed July 2022*)

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory developed tests (LDTs) must meet general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Xpresys Lung test and Xpresys Lung 2 (BDX-XL2) (Integrated Diagnostics [Indi], purchased by Biodesix) Nodify XL2, Percepta® Bronchial Genomic Classifier (Veracyte) and REVEAL Lung Nodule Characterization (MagArray) are available under the auspices of CLIA. Laboratories that offer laboratory developed tests (LDTs) must be licensed by CLIA for high complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

PRIOR APPROVAL

Not applicable.

POLICY

Gene Expression Profiling (GEP)
Gene expression profiling on bronchial brushings in individuals with indeterminate bronchoscopy results from undiagnosed pulmonary nodule(s) including but not limited to Percepta® Bronchial Genomic Classifier is considered **investigational**.

Direct evidence of the clinical utility for gene expression profiling (GEP) of bronchial brushings is lacking. Indirect evidence of the clinical utility suggests that Percepta® Bronchial Genomic Classifier has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. However, long-term follow-up data would be required to determine the survival outcomes in individuals with a missed diagnosis of lung cancer at earlier, more treatable stages. Also, no professional society guidelines to include the National Comprehensive Cancer Network (NCCN), guidelines indicate the utilization of gene expression profiling (GEP) on bronchial brushings in the management of individuals with indeterminate bronchoscopy results for undiagnosed pulmonary nodule(s). The evidence is insufficient to determine the effects of the technology on net health outcomes.

Plasma-Based Proteomic Screening
Plasma-based proteomic testing utilized as a screening or diagnostic tool in individuals with undiagnosed pulmonary nodule(s) detected by imaging, is considered **investigational** to include but not limited to the following tests:

- Early CDT® Lung Test
- Nodify CDT (0360U)
- Nodify XL2™ including the following prior generations of this test:
    - Xpresys Lung
    - Xpresys Lung 2 [BDX-XL2]
- REVEAL Lung Nodule Characterization

Based on review of the peer reviewed medical literature while trial results are promising further clinical studies are warranted to more broadly assess the impact of these tests on clinical decision making, by accurately identifying individuals who are most likely to benefit from serial surveillance or early treatment, while reducing the rate of false-positive results, and unnecessary interventions, Also, long-term follow-up is needed to include the rate of lung cancer deaths prevented using this test to further verify this an effective risk assessment of lung cancer. Also, no professional society guidelines to include the National Comprehensive Cancer Network (NCCN), guidelines indicate the utilization of plasma-based proteomic screening in the management of individuals with undiagnosed pulmonary nodule(s). The evidence is insufficient to determine the effects of this technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 84999 Unlisted chemistry procedure (*when specified for Percepta® Bronchial Genomic Classifier or EarlyCDT Lung*)
- 0080U Oncology (lung), mass spectrometric analysis of galectin-3 binding protein and scavenger receptor cysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule speculation status and nodule location) utilizing plasma, algorithm reported as a categorical probability of malignancy (Nodify XL2 [*including the following prior generation of this test: Xpresys Lung 2 [BDX-XL2]*)
- 0092U Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy (*when specified for REVEAL Lung Nodule Characterization*)
- 0360U Oncology (lung), enzyme-linked immunosorbent assay (ELISA) of 7 autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, MAGE A4, and HuD), plasma, algorithm reported as a categorical result for risk of malignancy (*Nodify CDT®)*

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POLICY HISTORY		
Date	**Reason**	**Action**
August 2022	Annual Review	Policy Revised
August 2021	Annual Review	Policy Revised
November 2020	Annual Review	Policy Renewed
August 2019	Annual Review	Policy Revised
August 2018	Annual Review	Policy Revised
August 2017	Annual Review	Policy Revised
September 2016		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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