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Original Article

Impact of an integrated classifier using biomarkers, clinical and imaging factors on clinical decisions making for lung nodules

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Background: An integrated classifier that utilizes plasma proteomic biomarker along with five clinical and imaging factors was previously shown to be potentially useful in lung nodule evaluation. This study evaluated the impact of the integrated proteomic classifier on management decisions in patients with a pretest probability of cancer (pCA) ≤50% in "real-world" clinical setting.

Methods: Retrospective study examining patients with lung nodules who were evaluated using the integrated classifier as compared to standard clinical care during the same period, with at least 1-year follow-up.

Results: A total of 995 patients were evaluated for lung nodules over 1 year following the implementation of the integrated classifier with 17.3% prevalence of lung cancer. 231 patients met the study eligibility criteria; 102 (44.2%) were tested with the integrated classifier, while 129 (55.8%) did not. The median number of chest imaging studies was 2 [interquartile range (IQR), 1–2] in the integrated classifier arm and 2 [IQR, 1–3] in the non-integrated classifier arm (P=0.09). The median outpatient clinic visit was 2.00 (IQR, 1.00–3.00) in the integrated classifier arm and 2.00 (IQR, 2.00–3.00) in the non-integrated classifier (P=0.004). Fewer invasive procedures were pursued in the integrated classifier arm as compared to non-integrated classifier respectively (26.5% *vs.* 79.1%, P<0.001). All patients in the integrated classifier arm with post-pCA (likely benign n=39) had designated benign diagnosis at 1-year follow-up.

Conclusions: In patients with lung nodules with a pCA ≤50%, use of the integrated classifier was associated with fewer invasive procedures and clinic visits without misclassifying patients with likely benign lung nodules results at 1-year follow-up.

Keywords: Lung nodules; biomarker; pulmonary procedures

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Introduction

The estimated incidence of pulmonary nodules in the United States is around 1.6 million per year. However, the true incidence is likely much higher due to increased availability and use of chest imaging as well as lung cancer screening programs (1-3). The diagnosis and management of pulmonary nodules poses a challenge for both clinicians and patients (1,4). Current guidelines recommend that evaluation of such nodules is based upon the pretest probability of malignancy and choosing the appropriate management pathway with the intention to avoid unnecessary diagnostic procedures in those with benign disease and expedite diagnosis and treatment in those with malignancy (5-8). Thus, patients with very low-risk nodules may be managed with chest imaging surveillance, whereas patients with high-risk nodules may proceed directly to definitive therapy with surgical excision. Unfortunately, most patients with nodules fall in the "intermediate risk" category for cancer spectrum. This represents a diagnostic dilemma as multiple options are available including additional diagnostic interventions (bronchoscopy with biopsy or percutaneous lung biopsy), continued imaging surveillance or surgical resection. Therefore, complementary noninvasive diagnostic testing might improve risk stratification and could assist in subsequent management decisions as well as reduce patients' exposure to unnecessary invasive procedures by shifting benign lung nodules into surveillance.

Several panels of proteins (13-protein blood test) have been proposed to differentiate benign from malignant lung nodules using multiple reaction monitoring mass spectrometry with a 90% negative predictive value (NPV) for benign nodules (9). Another study evaluated a 5-marker subset of the original 13 proteins together with 6 normalization markers showing clinical utility based on the test's NPV potentially sparing invasive procedures for 31.8% of subjects (10). Recently, it was shown that the accuracy of two plasma proteins [galectin-3 binding protein (LG3BP) and scavenger receptor cysteine-rich type 1 protein M130 (C163A)] which are independently linked to lung cancer and the inflammatory response to cancer could be optimized for evaluating lower risk nodules by integrating them with five clinical risk factors (nodule location, size, spiculation and patient's age and smoking history) in the intended use population with probability of cancer (pCA) ≤50% (9-11). Using decision tree analyses, this integrated model, termed Nodify XL2™ test (Biodesix) has been commercially available to provide a post-test probability of a lung nodule being benign. The relative contribution of the component elements of the integrated classifier have already been published previously in the PANOPTIC trial (12).

The PANOPTIC study was a multicenter observational study designed to clinically validate the integrated classifier algorithm in the intended use population. In nodules with pCA ≤50%, the classifier correctly identified benign nodules with sensitivity 97%, specificity 44%, and negative predictive value (NPV) 98% at 1-year follow-up (12), with similar accuracy confirmed at 2-year follow-up period (13). Furthermore, the study estimated that the integrated classifier could enable a 40% reduction in invasive procedures within the intended use patient population and only 3% of malignant nodules would be misclassified. Such studies only modeled the theoretical clinical utility of such lung biomarker. To our knowledge, our study is among the first to evaluate the impact on clinical decision-making in a "real-world" setting.

The goal of this study was to evaluate the clinical impact of integrated classifier in "real-world" setting against a control arm. We have also explored whether patient -centered communication using educational video and open discussion with caregiver can improve understanding of lung biomarker testing in a subset of low-income, vulnerable smokers. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-42/rc).

Highlight box

Key findings

- An integrated classifier biomarker combining two plasma proteins with five clinical/imaging factors can improve risk stratification to shift benign nodules into surveillance, thereby minimizing invasive procedures.

What is known and what is new?

- Integrated classifier biomarker was shown to be potentially useful in clinical validation studies.
- This clinical utility study investigated the impact of integrated classifier biomarker in a real-world setting.

What is the implication, and what should change now?

- Integrated classifier biomarker can be incorporated in diagnostic workup of pulmonary nodules.

Methods

Study design

A multicenter, retrospective cohort study evaluating the performance of the integrated classifier test comprising two proteins and five clinical risk factors over a period of 2 consecutive years (2019 to 2021). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval was obtained by each institution (Beth Israel Deaconess Medical Center, Tulane Medical Center, and Einstein Medical Center) prior to study commencement (Nos. 21-402, 2021-740, and 2021-733). Individual informed consent was waived in all the three institutions due to the retrospective nature of the study. An informative sheet was provided to each participant included in the Survey assessment per IRB request. No funding provided for the elaboration of this project. A decision to use integrated classifier was left to the physician managing lung nodule.

Patient selection

Eligible patients were:

(I) ≥40 years old with incidental solid pulmonary nodules between 8 to 30 mm in diameter without associated mediastinal or hilar lymphadenopathy presenting within 60 days of the baseline CT scan to a pulmonologist;
(II) The pre-test risk of cancer as determined by the Mayo risk prediction algorithm (14) is 50% or less;
(III) Has available follow up data for at least 1-year period.

Patients were ineligible if they had any of the following:

(I) Any attempt at a previous biopsy of the nodule in question;
(II) Current or previous diagnosis of any cancer within 5 years of lung nodule detection (except for nonmelanoma skin cancer);
(III) Nodule of concern is part-solid, ground glass opacity or detected during lung cancer screening;
(IV) Any patient treated empirically with radiation and/or chemotherapy for a suspected malignancy without a confirmatory diagnosis.

Plasma proteomic analysis

Proteomic analysis of two plasma proteins, LG3BP and C163A, was performed by using multiple reaction monitoring mass spectroscopy (9,10). Results were integrated with the five clinical risk factors [age (in years), smoking status (never or current/former), nodule diameter (largest diameter), edge characteristics (spiculated or other), and location (upper or other)] to yield a posttest probability of a lung nodule being benign (11).

The validated Nodify XL2 algorithm has two performance thresholds that produced three categories for test results: Likely Benign, Reduced Risk of Cancer and Indeterminate (Table S1) (11,12).

(I) Likely benign test result which produces a 98% negative predictive value (NPV) with a sensitivity of 97% and specificity of 44%;
(II) The indeterminate result is a non-actionable label where physicians are recommended to manage the nodules without consideration of the Nodify XL2 label;
(III) The reduced risk subgroup falls in between the upper and lower cut-offs of the likely benign and indeterminate labels. These patient results include a range of test performance thresholds that are statistically different from the indeterminate group, but do not achieve the preferred 98% NPV score for a likely benign result.

Decision aid

A decision aid consisting of an educational video informing patients about lung nodule along with benefits and harms of lung biomarker testing was used before patients meet the clinician. The web-based decision aid was designed for an eighth-grade level. Furthermore, participants were able to ask questions to clinicians following the video during their clinic visit.

Survey

Participants self-completed brief survey before and after the educational video regarding attitudes and knowledge of lung biomarker testing. Questions were adapted from prior studies (15-17). Given the small sample size, answers to questions were frequently dichotomized for analysis. We assessed the overall percentage of questions regarding benefits and harms that were answered correctly, grouping "unsure" answers with incorrect responses. Answers about attitudes regarding lung biomarker testing grouped "strongly agree" or "agree" together compared with "disagree", or "strongly disagree" (Tables S2,S3).

Study objectives

Primary objective

To assess whether a reduction in the proportion of benign lung nodules experiencing invasive procedures was present in the integrated classifier arm as compared to the non-integrated classifier arm.

Secondary objectives

(I) To assess whether the number of malignant lung nodules routed to CT surveillance was increased as compared to the non-integrated classifier arm where standard of care for nodule management is implemented;
(II) To evaluate the number or chest imaging and outpatient clinic visits in the integrated classifier arm as compared to the non-integrated classifier arm.

Other objectives

To perform a pilot survey in a low-income, racially diverse population, assessing participants' knowledge and attitudes to a web-based tool as well as open discussion with physicians regarding lung biomarker testing for solitary lung nodules.

Definitions

Benign nodules were defined if any of the following:

(I) Definitive pathologic diagnosis or alternative diagnosis that explained symptoms leading to lung cancer suspicion;
(II) Radiographic resolution;
(III) No evidence of growth according to chest imaging ≥1 year period and physician had no further suspicion regarding possible lung cancer diagnosis.
(IV) Malignant diagnosis was based on histopathologic findings. Vulnerable populations are defined by race/ethnicity, education, and socioeconomic status (18,19).

Data collection

Data collected for study subjects included:

(I) Demographics;
(II) Clinical history relevant to lung nodule;
(III) Diagnostic procedures and results;
(IV) Number of chest imaging and clinic visits related to lung nodules;
(V) Surveys before and after educational video/open discussion.

Statistical analysis

Data was analyzed using STATA Release 14 (Stata-Core, College Station, TX, USA). Descriptive statistics were used to summarize findings. Continuous outcomes were presented as means or medians depending on the normality assessment Shapiro-Wilk test, whereas dichotomous outcomes are presented as proportions. Univariate analysis was performed using chi-square testing for dichotomous outcomes and *t*-test or Kruskal Wallis test for continuous outcomes depending on normality. P-values were deemed significant if less than 0.05. Regarding the survey, the same questionnaire was conducted before and after the medical encounter with the specialist, with an initial true/false section followed by a multiple-choice section. For the first part of the questionnaire with true and false answers, a McNemar's test was performed to evaluate statistical significance with the change in proportions. For the second part of the questionnaire, participant responses were pooled into two groups by dichotomizing answers to either favorable response, corresponding to "agree" or "strongly agree", or unfavorable response corresponding to "disagree" or "strongly disagree". The proportion of participants responding with a favorable answer, before and after the course, was computed. A McNemar's test was also performed to evaluate statistical significance with the change in proportion.

Results

A total of 995 patients were evaluated for lung nodules following the implementation of the integrated classifier over the study period of one year. A total of 231 patients met inclusion criteria and were eligible for analysis (*Figure 1*).

The demographic characteristics are shown in *Table 1*. The median age in the integrated classifier arm was 66 with interquartile range (IQR, 61–72) and median age in the non-integrated classifier arm was 71 (IQR, 61–77). A total of 52.9% were men in integrated classifier arm and 44.2% in the control arm. Both groups had significant smoking histories. A total of 60.8% were smoker (active or former) in integrated classifier arm and 78.3% in the control arm. No differences were observed in nodule characteristics between patients in the integrated classifier or control arm (n=231). The prevalence of malignancy was 17.3%, with the majority being adenocarcinoma histology (60%). There was no significant difference between lung nodule size (11.5 *vs.* 13 mm; P=0.09), number of nodule (1 *vs.* 1, P=0.08), upper

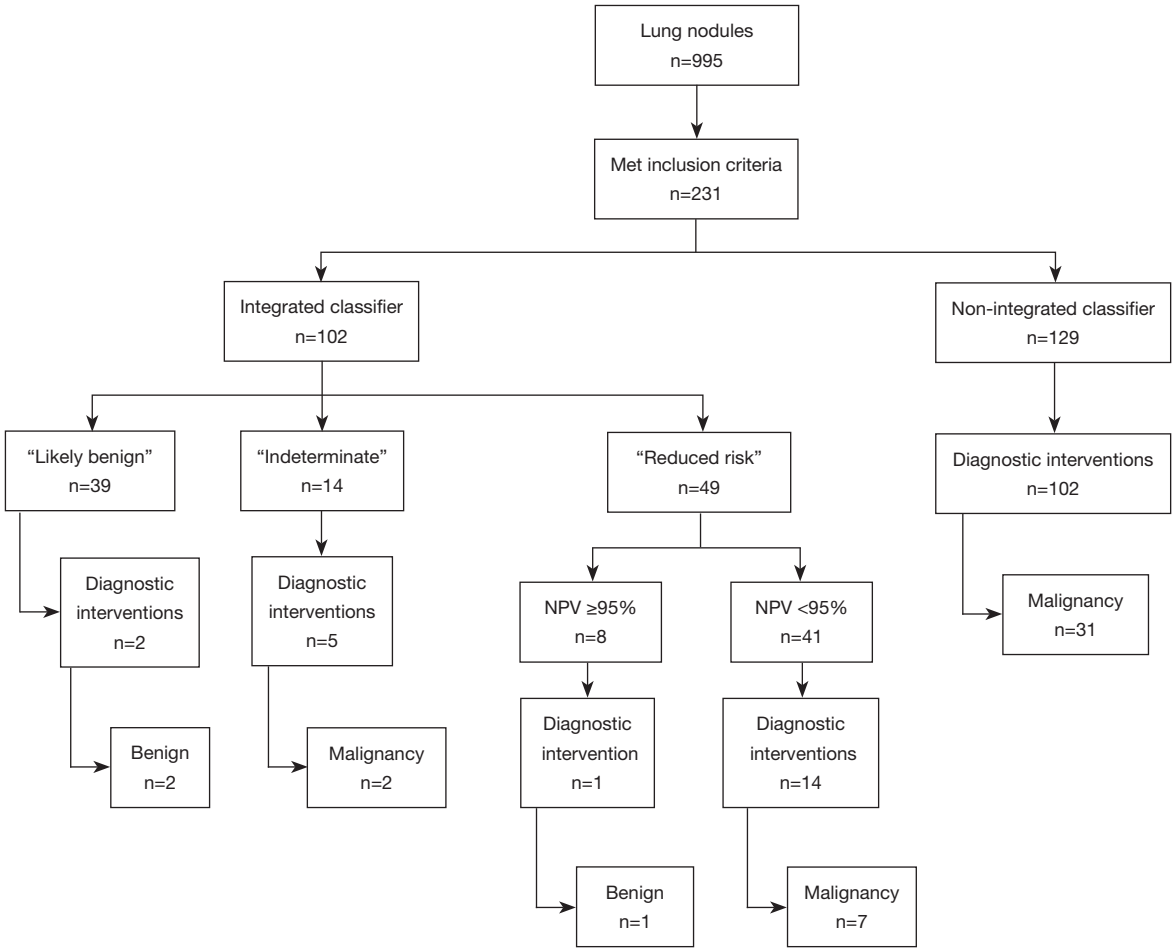

Figure 1 Flow diagram of the study. NPV, negative predictive value.

Table 1 Demographics of patients with lung nodule pCA ≤50%

Variables	Integrated classifier (n=102)	Non-integrated classifier (n=129)	P value
Age in years, median (IQR)	66.00 (61.00–72.00)	71.00 (61.00–77.00)	0.004
Men, n (%)	54 (52.9)	57 (44.2)	0.23
Former/current smoker, n (%)	62 (60.8)	101 (78.3)	0.006
Nodule size in mm, median (IQR)	11.50 (9.00–16.00)	13.00 (9.00–19.00)	0.09
Number of nodules, median (IQR)	1.00 (1.0–2.00)	1.00 (1.00–2.00)	0.08
Upper lobe nodule location, n (%)	62 (60.8)	71 (55.0)	0.24
Spiculation, n (%)	31 (30.4)	48 (37.2)	0.33

pCA, probability of cancer; IQR, interquartile range.

Table 2 Clinical outcomes of patients with lung nodule pCA ≤50%

Variables	Integrated classifier (n=102)	Non-integrated classifier (n=129)	P value
Chest imaging, median (IQR)	2.00 (1.00–2.00)	2.00 (1.00–3.00)	0.09
Number of clinic visits, median (IQR)	2.00 (1.00–3.00)	2.00 (2.00–3.00)	0.004
Diagnostic interventions, n (%)	22 (21.6)	102 (79.1)	<0.001

pCA, probability of cancer; IQR, interquartile range.

lobe location (60.8% *vs.* 55%, P=0.24) or spiculation (30.4% *vs.* 37.2%, P=0.33) in both groups.

The clinical outcomes of chest imaging, clinic visit, and procedural diagnostic interventions are shown in *Table 2*. There was no statistical difference between chest imaging use in integrated classifier group as compared to the non-integrated classifier group [2 (IQR, 1–2) *vs.* 2 (IQR, 1–3), P=0.09]. However, the number of clinic visits [2 (IQR, 1–3) *vs.* 2 (IQR, 2–3), P=0.004) as well as the procedural utilization (21.6% *vs.* 79.1%; P<0.001) was significantly less in the integrated classifier group without misclassifying patients with malignant nodule in the integrated classifier arm with likely benign results at 1-year follow-up.

In the integrated classifier group, 39 of 102 (38.2%) patients had a likely benign result after integrated classifier testing, 2 patients underwent diagnostic intervention with benign findings with all patients designated as having a benign diagnosis at 1-year follow-up. Also, 14 of 102 (13.7%) patients had indeterminate results following integrated classifier testing, 5 underwent diagnostic interventions, 2 had diagnosis of adenocarcinoma, and the rest had benign diagnosis at the 1-year follow-up. Finally, 49 (48%) patients had a reduced risk result after integrated classifier testing: 8 patients had NPV ≥95% and 41 had NPV <95%. A total of 15 underwent diagnostic interventions :1 in the category of NPV ≥95% and 14 in the category of NPV <95%. Seven had a final diagnosis of malignancy: 6 adenocarcinoma and 1 carcinoid tumor and all were in the group with NPV <95%, whereas the rest had benign diagnosis at the 1-year-follow-up.

In the non-integrated classifier group, 102 of 129 patients underwent diagnostic interventions and 31 had a final diagnosis of malignancy: 16 adenocarcinoma, 8 squamous cell,3 nonspecific non-small cell, 3 carcinoid and 2 small cell lung cancer. Also, 16 of the 102 interventions were non-diagnostic requiring additional diagnostic interventions (7 had final diagnosis of malignancy and 9 had final benign diagnosis) and 55 had benign diagnosis on 1-year follow-up.

We selected 40 vulnerable patients to perform a survey before and after participation in a patient centered communication that included an educational video and opportunity to ask clinicians questions regarding lung nodule and biomarker testing. 40% of participants were women and 58.8% completed up to high school education. About 61.8% reported an annual income <$50,000 and 53.9% were nonwhite.

Participants demonstrated improved knowledge and attitude about lung nodule and use of biomarker after watching an educational video and spending time asking questions about biomarkers, albeit not statistically significant (*Tables 3*,*4*). Participants were able to recognize that lung nodules are quite common and might be an incidental finding, with perception improved by 25%. The most notable was improvement in knowledge that most lung nodules are not cancerous, with perception improved by 32.5%. More participants endorsed that biomarker could identify patients with likely benign nodule as well as decide whether further intervention is needed, with perception improved by 30% and 17.5% accordingly. Also, participants recognized that a biomarker might support clinical decision making at the end of the discussions, increasing from 55% before to 82.5% afterwards. Most participants who watched the educational video and asked questions afterwards agreed or strongly agreed that biomarker testing might help with clinical care (improved by 22.5%), were more aware about purpose of biomarker testing (improved by 22.5%), were better informed that a benign test made lung cancer diagnosis less likely (improved by 17.5%) and were less worried regarding lung nodule finding on chest imaging (decreased by 20%) or need for additional interventions (improved by 25%).

Discussion

A biomarker to rule in or out lung cancer among patients with indeterminate pulmonary nodules would have enormous clinical benefit in reducing the rate of unnecessary thoracic surgery on benign nodules, invasive

Table 3 Participant knowledge regarding lung biomarker screening at baseline and after web-based tool: n=40 participants

True/false questions	Choosing response marked as "true", n (%)		P value
	Baseline	After web-based tool	
Lung nodules are quite common and may be an incidental finding	25 (62.5)	35 (87.5)	N/S
Lung nodules are usually cancerous	28 (70.0)	15 (37.5)	N/S
Biomarker testing helps identify patients with likely benign nodule	20 (50.0)	32 (80.0)	N/S
Biomarker testing helps physician decide whether invasive intervention is needed	19 (47.5)	26 (65.0)	N/S
Biomarker testing supports clinical decision-making	22 (55.0)	33 (82.5)	N/S

N/S, none significant.

Table 4 Participant attitudes regarding lung biomarker screening at baseline and after web-based tool: n=40 participants

Statement	Strongly agree or agree, n (%)		P value
	Baseline strongly agree or agree	After web-based tool strongly agree or agree	
I am worried about the abnormal finding reported on chest imaging	26 (65.0)	18 (45.0)	N/S
I am worried that additional interventions are needed for lung nodule	29 (72.5)	19 (47.5)	N/S
I am aware about the purpose of undergoing lung biomarker testing	12 (30.0)	21 (52.5)	N/S
A benign biomarker result will make me less worried about developing lung cancer	23 (57.5)	30 (75.0)	N/S
The implementation of lung biomarker will improve my clinical care	22 (55.0)	31 (77.5)	N/S

N/S, none significant.

procedures, the time to diagnosis and cost. The adoption of new biomarker into clinical practice requires a learning curve for optimal utilization, clinical utility study as well as ensuring effectiveness while minimizing harm to the intended use population (20,21).

This study is among the first clinical "real-world" trial evaluating the impact of an integrated blood proteomics classifier, a clinically validated diagnostic tool that improves the diagnostic capability in patients with pulmonary nodules at risk for lung cancer (11,12). In patients with pCA ≤50%, a likely benign integrated classifier result, decreased overall invasive procedures by 57.5% without missing a malignant diagnosis at 1-year follow-up as compared to the arm not using an integrated classifier. Although the number of chest imaging was not statistically different between both groups, the number of clinic visits was less in the integrated classifier arm.

Furthermore, we conducted a pilot survey to evaluate patients' knowledge and attitude towards lung biomarker testing. We showed that decision aid-facilitated discussions might help improve participants' understanding of lung nodules and the potential role of biomarker testing. After watching an educational video and having an active discussion on the topic, participants could identify that lung nodules are common, not usually cancerous, were less anxious regarding abnormal chest imaging, and demonstrated understanding that biomarker testing can help in decision making in workup and management leading to possible fewer further interventions. Although the results were not statistically significant, but they are clinically relevant.

The decision to intervene on a lung nodule via invasive diagnostic procedures incorporates the pretest probability of malignancy as well as patient and physician preferences. Validated prediction models such as Mayo and Brock that are widely used to assess pretest probability of malignancy can over-estimate the probability of malignancy as documented in a large, population-based observational study (22). Overestimation of the probability of cancer can have important implications in clinical practice by leading physicians to order unnecessary diagnostic tests. Thus, adding biomarker testing with both physician and patient knowledge about benefits/harms of such a test can help inform better decision making. The use of integrated classifier offers several advantages. First, it outperformed validated lung nodule risk models such as Mayo, Brock, and VA as well as physician pCA in the intended use population with pCA ≤50% (12-14,23,24). Second, it does not require patients to undergo routine bronchoscopy as in the case of bronchial-airway gene expression classifier, another available rule-out biomarker (21). Third, despite that most indeterminate lung nodules are benign, both physicians and patients remain anxious, which can lead to further unnecessary work up (25). A recent study assessed the diagnostic costs leading up to a lung cancer diagnosis in patients with abnormal chest imaging. A total of 19% underwent a biopsy and 43% were not diagnosed with lung cancer during follow-up. Among patients with eventually benign lung nodule diagnosis, the median diagnostic cost per patient for those with versus without biopsy was around 28 times higher. Adverse events significantly increased the average cost per biopsy up to 4-fold (26). Finally, the adoption of a non-invasive biomarker can be cost-effective as most of the cost is due to diagnostic interventions in patients with indeterminate lung nodules (26). Another commercially available test that is EarlyCDT-Lung. It consists of seven autoantibody panel that underwent multiple clinical validity studies and in a recent post marketing audit of over 1,600 patients presenting with a nodule of approximately 8–30 mm, showed a sensitivity of 41% at a specificity of 87% (27). Also, a cost effectiveness study indicated that the use of such test is around $24,000 per quality-of-life adjusted life year gained (28).

Results from this study highlight aspects from the physician as well as patient perspectives that might play a role in the adoption of biomarker testing. First, the use of a biomarker could impact clinical decisions potentially leading to reduced health care utilization (clinic visits, invasive procedures). Second, using utilizing decision aids and engaging in active discussions with patients can improve shared decision-making regarding lung nodules and further enhance implementation of a biomarker in clinical practice. Finally, a likely benign result in integrated classifier can decrease anxiety and uncertainty for both patients and clinicians managing lung nodules.

A biomarker test should add value to standard clinical practice and lead to a change in clinical decision making, from an invasive procedure to surveillance for instance. In patients with indeterminate lung nodules where imaging and clinical factors alone cannot formulate a clinical decision, an integrated classifier might be clinically meaningful as shown in our current study where 38.2% of patients were reclassified to the "likely benign" category and only 2 patients underwent invasive testing while the majority were spared any addition intervention without affecting malignant diagnosis in 1-year follow-up.

Furthermore, patients experience distress and inadequate communication about pulmonary nodules and their evaluation (29). Such distress can be associated with decreased adherence for clinic follow-up and imaging. However, many clinicians are unaware of the degree to which some patients are affected by the finding of a pulmonary nodule (29). A decision aid could improve patient-clinician communication regarding lung nodule as well as available biomarker that could help with shared decision making.

This study has several strengths. First, to the best of our knowledge, this study is the first multicenter, clinical study across several geographical locations to assess the clinical impact of an integrated blood biomarker for the evaluation of pulmonary nodules. Second, we are among the first to evaluate the use of a biomarker from the patient perspective in high-risk populations including diverse racial groups and low-income populations. However, we acknowledge that additional educational and behavioral considerations need to be studied and incorporated to offer insight about implementing a biomarker into clinical practice.

The present study has limitations. First, the use of an integrated classifier was retrospectively studied in clinical practice; however, a prospective randomized study to assess changes in practice is warranted and underway to evaluate such impact in clinical practice (NCT04171492). Second, patients were followed up to 1-year outcomes for stable nodules, in contrast to traditional 2 years surveillance for nodule stability. This was chosen as 1 year of chest imaging

stability demonstrated no growth in nodules stable on subsequent 2-year follow-up in a research setting (13,30). Third, due to retrospective nature of the study with 1-year follow-up, there is a possibility that patients in the integrated classifier arm with reduced or indeterminate risk might eventually had malignant nodule diagnosis and thus it is essential to continue chest imaging surveillance for such patients. Finally, advanced age and smoking history were more common in the non-integrated classifier arm which might have impacted our results.

Conclusions

In this real-world retrospective multicenter study, a likely benign integrated classifier results reduced invasive procedures without missing a malignant diagnosis. These findings are consistent with prior clinical validation studies and our findings indicate that using this biomarker has a positive impact on patient management. Furthermore, engaging patients in shared decision-making regarding lung nodule management was assisted by biomarker testing. Our surveys suggest the educational video helped patients understand nodule evaluations and the use of a biomarker. The use of the biomarker may have also reduced patient anxiety and future studies will help further identify tools from patient perspectives to implement biomarker testing.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-42/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-42/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-42/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-42/coif). FK received honoraria from Biodesix and Veracyte for educational events. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval was obtained by each institution (Beth Israel Deaconess Medical Center, Tulane Medical Center, and Einstein Medical Center) prior to study commencement (Nos. 21-402, 2021-740, and 2021-733). Individual informed consent was waived in all the three institutions due to the retrospective nature of the study.

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Supplementary

Table S1 Performance characteristics of Nodify XL2

Test result	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Likely benign	98% (92–100%)	97% (82–100%)	44% (36–52%)
Reduced risk	97% (91–100%)	93% (77–99%)	49% (41–57%)
	96% (90–99%)	90% (73–98%)	54% (45–62%)
	95% (89–99%)	86% (68–96%)	55% (46–63%)
	94% (87–98%)	83% (64–94%)	56% (47–64%)
	93% (86–98%)	79% (60–92%)	57% (44–65%)
	92% (85–96%)	76% (56–90%)	58% (49–66%)
	91% (84–96%)	69% (49–85%)	64% (56–72%)
	90% (84–95%)	55% (36–74%)	83% (75–88%)
Indeterminate	<90%	–	–

NPV, negative predictive value; CI, confidence interval.

Table S2 Lung biomarker questionnaire true/false assessment

Statements	True	False
Lung nodules are quite common and may be an incidental finding		
Lung nodules are usually cancerous		
Biomarker testing helps identify patients with likely benign nodule		
Biomarker testing helps physician decide whether invasive intervention is needed		
Biomarker testing supports clinical decision-making		

Table S3 Lung biomarker questionnaire agreement assessment

Statements	Strongly agree	Agree	Disagree	Strongly disagree
I am worried about the abnormal finding reported on chest imaging				
I am worried that additional interventions are needed for lung nodule				
I am aware about the purpose of undergoing lung biomarker testing				
A benign biomarker result will make me less worried about developing lung cancer				
The implementation of lung biomarker will improve my clinical care				

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