Assessment of Integrated Classifier's Ability to Distinguish Benign From Malignant Lung Nodules

Extended Analyses and 2-Year Follow-Up Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial

To the Editor:

Pulmonary nodules pose a diagnostic dilemma for clinicians and patients.[1] Guidelines for nodule management emphasize assessment of pretest probability for malignancy (pCA) in determining next steps.[2,3] The goal for nodule management is to avoid diagnostic procedures in those with benign disease and expedite diagnosis and treatment in those with malignancy. A rule-out biomarker can assist in improving risk stratification to shift benign nodules into surveillance, thereby minimizing invasive procedures.

An integrated proteomic biomarker combining two plasma proteins (LG3BP and C163A) with five clinical/imaging factors (age, smoking status, nodule size, edge, and location) was previously shown to be potentially useful in nodule patients with a pretest probability of malignancy of 50% or less. Using 1-year follow-up to determine benignity, the biomarkers accuracy reported a sensitivity of 97%, specificity of 44%, and negative predictive value of 98%. The biomarker was more accurate than physician and risk calculator assessments.[4] Here we report the 2-year follow-up results of the PulmonAry NOdule Plasma proTeomIc Classifier (PANOPTIC) trial and an extended analysis to those with multiple pulmonary nodules.

Methods

Design and Patient Enrollment

The prospective PANOPTIC trial[5] was conducted at 33 sites to validate the clinical performance of the integrated classifier Nodify XL2 test (Biodesix Inc., Boulder, CO). Details of trial design and test development have previously been published.[4,6] Briefly, patients age 40 years or older with a newly detected nodule 8 to 30 mm in diameter were included. Cancer diagnosis was by histopathology, and benign diagnosis was made by histopathology, radiographic resolution, or stability. The 1-year analysis population included 178 patients. Imaging data at 2 years minimum was available from 161 patients for this report. The presence and total number of nodules were noted from radiology reports and collected on case report forms.

Integrated Classifier and Performance Assessment

Factor analysis assessed the contribution of each clinical factor and the protein analytes. Classifier performance was compared with the validated Mayo, Veterans Administration, and Brock (1b) models.[7-9]

Data Analysis

Statistical analyses were performed using MATLAB, version 8.3.0.532 (MathWorks), MedCalc, version 16.4 (MedCalc Software bvba). McNemar's test was used for risk prediction model comparison with a fixed sensitivity or specificity. The Pearson correlation metric (r) was used to characterize strength of relation between the combined two-protein analytes and the strongest two clinical factors. Fisher exact test was used to compare single vs multiple nodules (>1), with $P < .05$ considered significant.

Results

Of the 392 patients included in the PANOPTIC study, 178 had a physician-assessed pCA of at least 50% (Fig 1). In patients with a pCA ≤ 50%, 149 (84%) were benign at year 1. At year 2, 10 patients were lost to follow-up, and seven had final visits that did not extend to 2 years. These 17 excluded patients had been categorized as benign at the 1-year interval, reducing the number of patients with benign nodules to 132 at the 2-year interval and leaving a total of 161 patients (90%) with data available for analysis.

All nodules designated as benign at year 1 remained benign by imaging (eg, stable or resolved) at year 2 with no change in pathologic diagnoses or nodule size by CT (Table 1).

Patients included in the trial could have more than one nodule on imaging studies, with the most suspicious selected as the index lesion. In the intended use group (n = 178), 101 (57%) had multiple nodules on CT imaging. There were on average three nodules (range, 1-10), and more than four indicated a shift to a higher probability of a

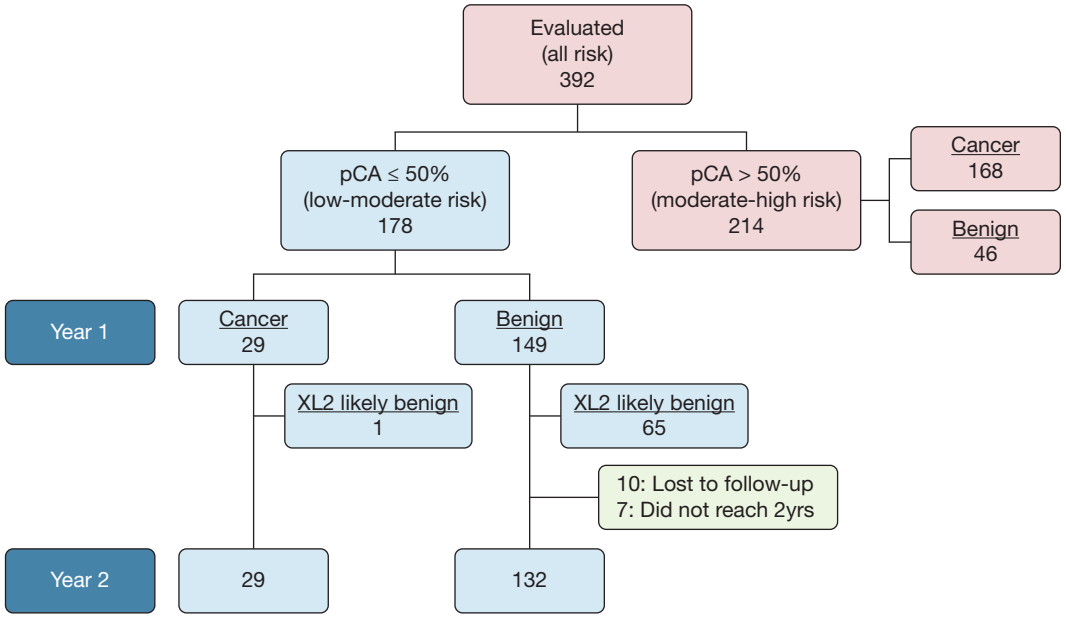

Figure 1 – *Diagnoses of subjects enrolled in PANOPTIC in the excluded group (pCA > 50%) and year 1 and year 2 results integrated classifier classifications in the intended use group (pCA ≤ 50%). PANOPTIC = Pulmonary Nodule Plasma Proteomic Classifier; pCA = probability of malignancy; XL2 = integrated classifier.*

TABLE 1] Demographics of PANOPTIC Patients With Benign Nodules at Years 1 and 2

Demographics	Benign at 1 Year	Benign at 2 Years	*P*
Patients	149	132	
Age, y	65.4 ± 1.78	66.7 ± 1.9	.83
Sex			
Male	83 (56%)	72 (55%)	
Female	66 (44 %)	60 (45%)	
Smoking history			
Never	36 (24%)	32 (24%)	
Former	83 (56%)	73 (55%)	
Current	30 (20%)	27 (20%)	
Avg	43.5 ± 7.1	44.0 ± 6.4	.93
Lung nodule			
Size	13.46 ± 0.78	13.56 ± 0.84	.87
Location			
Upper lobe	70 (47%)	63 (48%)	
Lower lobe	79 (53%)	69 (52%)	
Diagnoses			
Benign			
Granuloma	9 (6%)	9 (7%)	
Hamartoma	6 (4%)	6 (5%)	
CT stable/resolved	116 (78%)	100 (76%)	
Other	15 (10%)	17 (13%)	
NA	3 (2%)	0	

Statistical analysis used Fisher exact test, and $P < .05$ was considered significant. NA = not applicable; PANOPTIC = Pulmonary Nodule Plasma Proteomic Classifier.

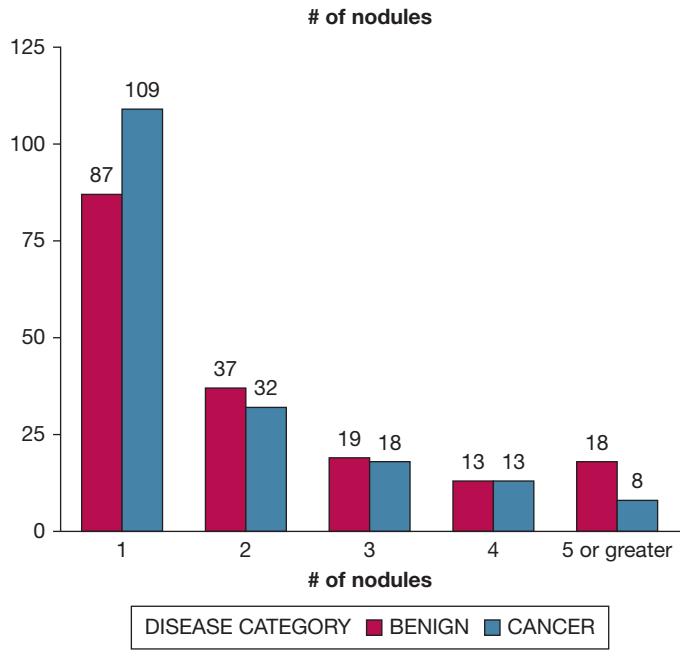

Figure 2 – *Cancer status (benign in red and cancer in blue), by nodule number for the evaluated PANOPTIC patients (n = 392). PANOPTIC = Pulmonary Nodule Plasma Proteomic Classifier.*

benign nodule (Fig 2). Patients with multiple nodules were older than those with a single nodule (P = .002). There was no significant difference in classifier performance between those with multiple nodules compared with those with 1 nodule (P = .164) (Table 2).

The area under the curve (95% CI) of the integrated classifier was 0.76 (0.69-0.82), outperforming the physcian pCA of 0.69 (0.62-0.76), Mayo 0.69 (0.62-0.76), VA 0.60 (0.53-0.67), and Brock 0.71 (0.63-0.77) in the lower-risk (pCA ≤ 50%) cohort.

Separation of the integrated classifier into the individual factors estimated the combined proteomic measure and nodule size as having the strongest contribution to the result (30% each). Age contributed 18%, with the remaining 22% coming from smoking status, edge characteristics, and nodule location in similar proportions.

TABLE 2] Performance of the Integrated Classifier in Patients With Solitary and Multiple Nodules With pCA ≤ 50% (N = 178)

Characteristic	All Patients	Multiple Nodules	Solitary Nodules	*P*
Patients	178	101	77	
Age, y	65.5 ± 1.6	67.7 ± 1.9	62.7 ± 2.5	.002
Sex				
Male	95 (53%)	52 (51%)	43 (56%)	.56
Female	83 (47%)	49 (49%)	34 (44%)	
Lung nodule				
Largest size, mm	14 ± 0.8	13.7 ± 1.0	14.3 ± 1.2	.49
Pathology				
Cancer	29 (16%)	16 (16%)	13 (17%)	
Benign	149 (84%)	85 (84%)	64 (83%)	.85
Test performance				
Sensitivity	97%	100%	92%	
Specificity	44%	47%	39%	
NPV	98%	100%	96%	.16

Statistical analysis used Fisher exact test, and $P < .05$ was considered significant. NPV = negative predictive value; pCA = probability for malignancy.

The Pearson correlation (r) suggested that the contribution of the protein analytes to the integrated classifier was not associated with either nodule size ($r = 0.045$) or patient age ($r = 0.063$).

Discussion

Although there has been precedent for reporting pulmonary nodule stability at 1 year, nodule management guidelines have recommended follow-up for 2 years for a nodule.[2] Here we present 2-year follow-up results from the first clinical validation study evaluating the performance of an integrated classifier, comprising blood protein analytes combined with clinical factors, to identify likely benign lung nodules. This study is both confirmatory and adds several important findings.

All nodules diagnosed as benign at year 1 remained benign at year 2, and the integrated classifier performance characteristics were maintained at year 2. These findings provide further support for using a 1-year follow-up for confirmation of benign nodules in a research setting.

Previous studies also have shown that patients present to pulmonologists with solitary and multiple nodules for evaluation at similar rates.[9,10] This study, although not powered to be conclusive, suggests that the classifier performs similarly regardless of nodule number. In addition, more than four or five nodues has been shown to be an indicator of a benign process, and the observational data displayed in Figure 2 is supportive.[9,10]

We expanded comparisons to validated risk prediction calculators in this analysis to include the Brock model, which was developed for a low-prevalence population. The integrated classifier outperformed all models in this cohort, especially as a rule-out test (>95% negative predictive value). In addition, the contribution of the protein analytes to classifier performance appears independent of nodule size and age, two predictors of nodule status. This study is limited by the exclusion of 17 patients who did not reach 2-year follow-up.

In conclusion, this 2-year follow-up extended analysis of the PANOPTIC trial confirms the accuracy of an integrated classifier in patients with indeterminate pulmonary nodules with pCA ≤ 50%, whether solitary or multiple. These results substantiate the case for a clinical utility study to determine how the integrated classifier impacts physician decision-making and patient outcomes.[11]

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