Clinical Utility of the Nodify XL2® Blood-Based Risk Classifier for Management of Benign Pulmonary Nodules in a Real-World Observational Study

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BACKGROUND AND STUDY DESIGN

Background: The Nodify XL2® integrated classifier (XL2) has been clinically validated[1] to improve accuracy in assessing probability of cancer (pCA) for lung nodules. This study evaluated the clinical utility of XL2 for invasive procedure reduction in patients with pre-test pCA ≤ 50%.

Research Question: Does the Nodify XL2 blood-based integrated classifier affect physician decision-making and as a result reduce the number of invasive procedures in patients with benign nodules?

Study Design and Methods: ORACLE is a prospective, multicenter observational registry study enrolling patients with recently detected 8-30 mm lung nodules (commenced October 2018). Registry patients' XL2 results were reported, and post-test procedures were recorded. A cohort of previously evaluated patients (between June 2015 and September 2018) who met the inclusion criteria and were not tested with XL2 were enrolled from each ORACLE site by chart review. Invasive procedure use on benign nodules (by radiographic resolution or stability for 1 year or specific benign histopathology) of registry patients was compared to chart review patients.

RESULTS

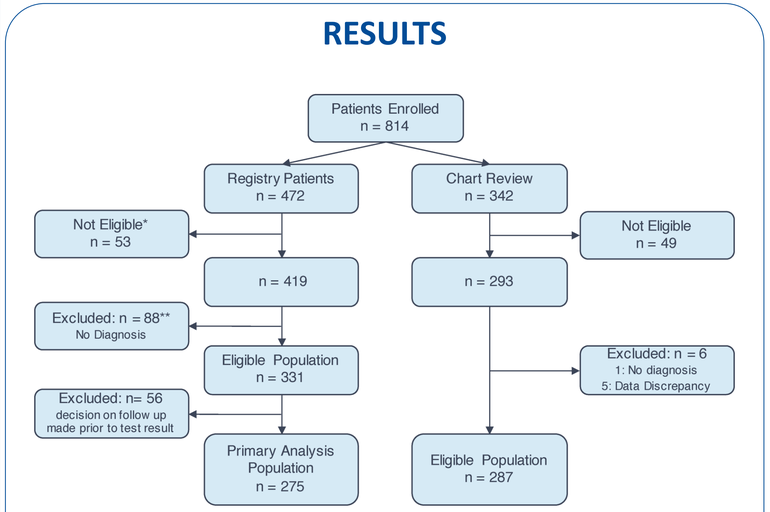

Figure 1 - Patient enrollment in ORACLE and eligibility for analysis. A total of 331 registry and 287 chart review patients met criteria for analysis, with 275 patients in the registry population eligible for analysis of primary aim (invasive procedure reduction). *Did not meet inclusion criteria (n = 38), consent withdrawn or not specified (n = 15). **Lost to follow-up (n = 32), 1 year follow-up incomplete / ongoing (n = 30), incomplete data collection (n = 17), deceased (n = 6), consent withdrawn (n = 2), other (non-lung) metastatic cancer detected (n = 1).

RESULTS

Table 1 Clinical characteristics of eligible (n = 618) and benign diagnoses (n = 449) patients enrolled in ORACLE.

	Eligible Population				Benign Population			
Characteristic	Registry (n = 331)	Chart Review (n = 287)	Total (n = 618)	*P* Value	Registry (n = 268)	Chart Review (n = 181)	Total (n = 449)	*P* Value
Definitive Diagnosis, n (%)				< 0.001	--	--	--	--
Benign	268 (81%)	181 (63%)	449 (73%)		--	--	--	--
Cancer	62 (19%)	106 (37%)	168 (27%)		--	--	--	--
Gender, n (%)				0.019				0.0036
Female	205 (62%)	151 (53%)	356 (58%)		164 (61%)	85 (47%)	249 (55.4%)	
Male	126 (38%)	136 (47%)	262 (42%)		104 (39%)	96 (53%)	200 (44.5%)	
Age (years)				0.001				
Mean (SD)	67.7 (8.7)	65.4 (9.1)	66.6 (8.9)		67.4 (8.8)	64.8 (9.8)	66.3 (9.3)	0.016
Nodule Location by Category, n (%)				0.24				0.85
Upper	153 (46%)	146 (51%)	299 (48%)		118 (43.9%)	82 (45.3%)	200 (44.5%)	
Other	178 (54%)	141 (49%)	319 (52%)		151 (56.1%)	99 (54.7%)	249 (55.5%)	
Nodule Size in mm				0.06				0.26
Mean (SD)	12.2 (4.1)	12.9 (4.3)	12.5 (4.2)		12.3 (4.1)	11.9 (3.9)	12.1 (4.0)	
Nodule Spiculation, n (%)				0.15				0.48
Yes	47 (14%)	53 (18%)	100 (16%)		34 (12.6%)	27 (14.9%)	60 (13.4%)	
No	284 (86%)	234 (82%)	518 (84%)		235 (87.4%)	154 (85.1%)	389 (86.6%)	
Smoking history, n (%)								0.021
Current Smoker	90 (27%)	110 (38%)	200 (32%)		60 (22%)	62 (34%)	122 (27%)	
Former Smoker	158 (48%)	125 (44%)	283 (46%)	0.02	135 (50%)	76 (42%)	211 (47%)	
Never Smoker	83 (25%)	52 (18%)	135 (22%)	0.003	73 (27%)	43 24%)	116 (26)	
Prior Cancer, n (%)				0.16				0.45
Yes	18 (5%)	9 (3%)	27 (4%)		12 (4%)	5 (3%)	17 (4%)	
No	313 (95%)	278 (97%)	591 (96%)		256 (96%)	176 (97%)	432 (96%)	
Pre-Test Risk (Mayo)				0.07				0.75
Minimum	3%	2%	2%		3%	2%	2%	
Median	19%	22%	20%		18%	18%	18%	
Maximum	50%	50%	50%		49%	50%	50%	

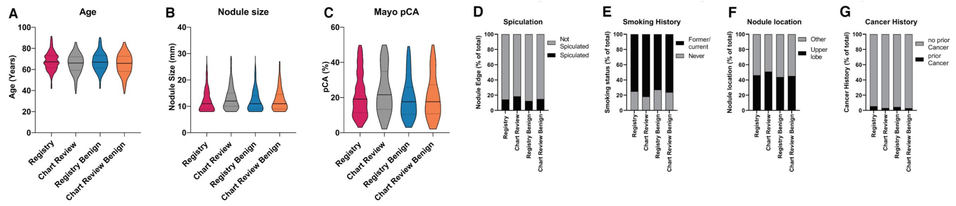

Figure 2 - Key clinical characteristics of ORACLE patients. Clinical characteristics and risk metrics for the total eligible registry (n = 331) and chart review (n = 287) populations and patients with definitive benign diagnosis in the registry (n = 269) and chart review (n = 181) cohorts. A, Age. B, Nodule size. C, Mayo SPN pCA. D, Spiculation. E, Smoking history. F, Nodule location. G, Cancer history.

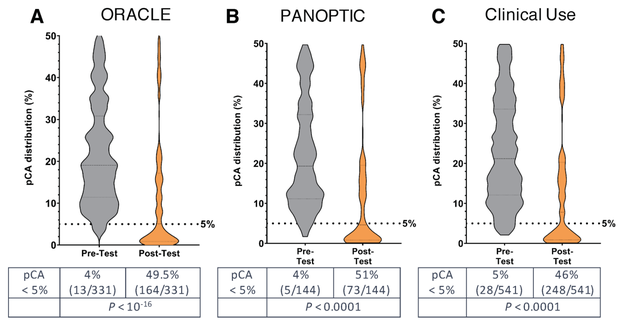

Figure 3 - Registry patient risk reclassification. Distribution of pre-test risk (Mayo SPN pCA) and post-test risk (XL2) classifications for A) the registry analysis population (n = 331) and concordance with B) prior clinical validation (PANOPTIC) (n = 144)[1] and C) clinical use cohorts (n = 541)[2].

Nearly half of patients managed with Nodify XL2 testing were reclassified from indeterminate to low risk in ORACLE (45.5%), in PANOPTIC clinical validation (46%), and in clinical use (41%) cohorts.

RESULTS

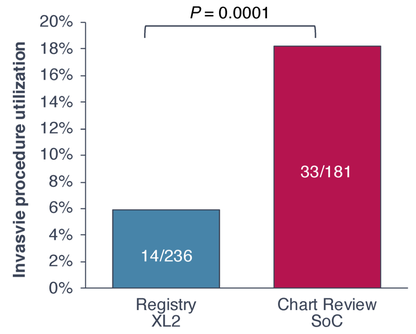

Figure 4 - Comparison of invasive procedure utilization before and after introduction of Nodify XL2 testing. Utilization of invasive procedures on nodules diagnosed benign with at least 1 year of follow-up in the registry primary analysis population (n = 236) and chart review analysis population (n = 181).

Registry invasive procedures
1 per 16.9 patients

Chart review invasive procedures
1 per 5.5 patients

Registry patients were 67% less likely to undergo an invasive procedure than those in the chart review cohort for a reduction of 1 invasive procedure per 8.13 patients tested (odds ratio 3.5, absolute risk difference 0.12, *P* = 0.0001).

CLINICAL IMPLICATIONS

- The Nodify XL2 blood-based, integrated classifier for patients with newly discovered lung nodules has demonstrated valuable clinical utility in a pragmatic, real-world clinical setting.
- Use of the test changed physician behavior and reduced invasive procedures on benign nodules by 67%.
- Integrated classifier testing is easily integrated into current management guidelines[3] (Figure 5).
- Reduction in invasive procedures on benign nodules may lead to improvement in patient outcomes, by reducing adverse events, complications, and hospitalizations associated with invasive procedures, and decrease costs to the patient and health care system.

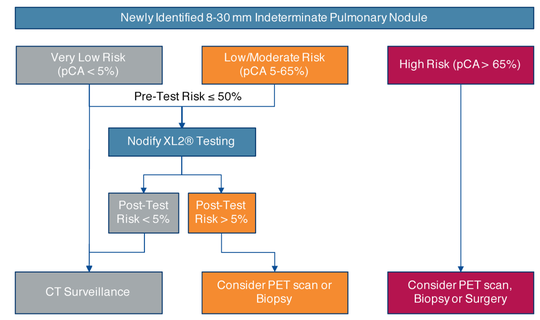

Figure 5 - Algorithm for indeterminate pulmonary nodule management integrating Nodify XL2 testing. Recommended strategy for integrating the Nodify XL2 classifier into the current paradigm of pulmonary nodule management recommended by ACCP[3] (modified). Note that patient preference is important in such clinical decision-making and may over-ride the suggested management strategy at patient and physician discretion.

Citations

1. Silvestri GA, Tanner NT, Kearney P, et al. Assessment of Plasma Proteomics Biomarker's Ability to Distinguish Benign From Malignant Lung Nodules: Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial. Chest. 2018;154(3):491-500.
2. Pritchett M, Sigal BW, Bowling MR, et al. First Look at the Distribution of Risk of Malignancy Pre and Post-Test Using a Blood-Based Biomarker in Patients with Pulmonary Nodules in a Real-World Observational Study. B110. Imaging And Molecular Biomarkers For Lung Cancer: American Thoracic Society; 2020:A4465-A4465.
3. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e93S-e120S.

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