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Review Article

Predictors of diagnostic accuracy in oncology imaging patients with pulmonary nodules

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Abstract

Background: Pulmonary nodules are detected incidentally or through screening in many chest CT examinations, and distinguishing the small minority that are malignant from the majority that are benign remains a central diagnostic problem in oncology imaging, since no single modality or threshold reliably separates the two.

Objective: This review synthesizes evidence on predictors of diagnostic accuracy in pulmonary nodule imaging, covering patient risk factors, nodule morphology, positron emission tomography, clinical prediction models, and radiomics and deep learning.

Methods: We synthesized peer-reviewed cohort studies, screening trials, meta-analyses, and guideline documents addressing diagnostic performance of CT, PET-CT, clinical risk models, and quantitative image analysis in patients with indeterminate pulmonary nodules.

Findings: Size, growth rate, and morphology such as spiculation and consistency are the strongest single predictors of malignancy; clinical models combining age, smoking history, and nodule features outperform size thresholds alone; PET accuracy declines below roughly 8-10 millimeters and in regions with high granulomatous disease prevalence; and radiomic and deep-learning approaches now approach or exceed conventional models in retrospective validation.

Conclusions: Diagnostic accuracy in pulmonary nodule imaging reflects several interacting predictors rather than any single test characteristic, and structured multivariable risk stratification combined with matched imaging technique outperforms reliance on any one modality or threshold in isolation.

Keywords: pulmonary nodule; diagnostic accuracy; computed tomography; PET-CT; radiomics

1. Introduction

A pulmonary nodule is one of the most common incidental findings in chest imaging, encountered on a substantial minority of chest CT examinations and, with the expansion of low-dose CT screening, on a large fraction of scans obtained specifically to find one. The great majority of nodules detected are benign granulomas, lymph nodes, or scars, while a small minority are early-stage cancers for which imaging-guided management determines whether the patient proceeds to curative resection or to surveillance that risks either unnecessary biopsy or delayed diagnosis. Because no single feature, threshold, or test achieves both high sensitivity and high specificity across the full range of nodules encountered in practice, diagnostic accuracy depends on the interaction of several predictors: patient-level risk factors, nodule morphology and growth behavior, imaging technique, functional imaging, and quantitative machine-learning analysis beyond what a radiologist reports by eye.

The modern era of structured nodule evaluation began with Bayesian probability-of-malignancy models built from clinical and radiographic variables [1], followed by the Mayo Clinic model of Swensen and colleagues, which formalized age, smoking history, prior extrathoracic cancer, diameter, spiculation, and location into a logistic-regression malignancy estimate that remains a benchmark for newer models [2]. Early single-arm screening cohorts such as the Early Lung Cancer Action Project had already shown that low-dose CT screening detected more early-stage, resectable cancers than chest radiography, motivating the randomized trials that followed [3]. The National Lung Screening Trial and the NELSON trial in Europe subsequently generated large prospective datasets on nodule prevalence, growth, and outcome that reshaped both the epidemiology of the problem and the models built to address it [4,5,6]. This review synthesizes what the literature establishes about the predictors of diagnostic accuracy in pulmonary

nodule evaluation: patient and epidemiologic risk factors, morphologic and volumetric CT features, the performance and limits of FDG-PET, structured clinical prediction models, and the contribution of radiomics and deep learning.

2. Patient-level and epidemiologic predictors

Pretest probability of malignancy is itself a strong determinant of how accurately any subsequent test performs, because positive and negative predictive value shift with disease prevalence in the population tested. Age, cumulative smoking exposure, and prior extrathoracic malignancy are the patient-level variables most consistently associated with risk, and each entered the original Mayo model as an independent predictor with a quantifiable odds ratio [2]. The National Lung Screening Trial demonstrated this at scale, enrolling more than 53,000 heavy smokers aged 55-74 and finding a baseline malignancy rate high enough to justify population screening, a finding that would not generalize to a low-risk population imaged the same way [4,5]. Screening-eligibility criteria refined by Tammemagi and colleagues using individualized risk prediction rather than simple age and pack-year cutoffs improved selection of who is screened in the first place, which upstream shapes the population in which any nodule-level test is later applied [7].

Family history, occupational exposures such as asbestos or radon, chronic obstructive pulmonary disease, and pulmonary fibrosis each independently modify pretest probability, and residence in a region with endemic granulomatous infection substantially raises benign nodule burden. This geographic effect matters as much for functional imaging as for pretest probability, since granulomas are frequently FDG-avid and generate false positives at rates that vary by region [8]. Sex differences in risk are smaller than age or smoking effects, and adenocarcinoma shows rising incidence among never-smokers, a subgroup for whom smoking-based risk

models systematically underestimate probability of malignancy [9].

3. Morphologic and volumetric predictors on CT

Nodule size is the single most consistently reported predictor of malignancy across cohorts, trials, and models, and is the variable around which most guidelines are structured [10,11]. Malignancy prevalence rises from well under 1% for nodules under 5 mm to a substantial minority above 20 mm, a gradient formalized quantitatively in the Brock University model derived from the Pan-Canadian Early Detection of Lung Cancer Study, where diameter, nodule count, spiculation, nodule type, and upper-lobe location were each independently predictive in a screening-detected population [12]. Because caliper measurement carries real inter-reader variability, particularly for small or subsolid nodules, the Fleischner Society issued CT measurement recommendations to reduce it, including averaging long- and short-axis diameters [13]; Revel and colleagues showed that two-dimensional measurements of small nodules carry enough variability to make apparent growth unreliable, motivating volumetric over linear measurement [14].

Morphology beyond size adds discriminatory information. Spiculated or lobulated margins are strongly associated with malignancy and are independent terms in both the Mayo and Brock models [2,12]; Erasmus and colleagues' review catalogued the morphologic descriptors, from margin to calcification pattern, a radiologist uses before any quantitative model is applied [15]. Diffuse, central, laminated, or popcorn calcification is reliably benign, whereas eccentric or stippled calcification does not exclude malignancy. Nodule consistency, solid, part-solid, or pure ground-glass, is especially important for adenocarcinoma spectrum lesions, since part-solid nodules carry higher malignancy rates than solid nodules of equal size, and the solid component correlates with invasive histology better than

overall diameter, a relationship exploited by quantitative texture analysis distinguishing preinvasive from invasive disease [16].

Table 1: Nodule-level predictors of malignancy on CT and their principal effect on diagnostic accuracy [10,12,15,16,17].			
Predictor	Benign pattern	Malignant-associated pattern	Effect on accuracy
Diameter	<6 mm	>20 mm	Strongest single predictor; basis for size-tiered guidelines
Margin	Smooth, well-defined	Spiculated, lobulated	Independent term in Mayo and Brock models
Consistency	Solid, stable	Part-solid with growing solid component	Solid-component growth predicts invasive histology
Calcification	Diffuse, central, popcorn	Absent or eccentric/stippled	High specificity for benignity when classic pattern present
Growth on serial CT	No volumetric change over 2 years (solid)	Volume doubling time <400 days	Integrates behavior over time; subsolid nodules are an exception

Growth rate, quantified as volume doubling time, integrates biological behavior over time rather than a single snapshot. Yankelevitz and Henschke showed that two years of CT stability is not the reliable benign indicator it was assumed to be for subsolid and part-solid nodules, since some adenocarcinoma-spectrum lesions grow only in density, reshaping the long-used two-year-stability discharge rule [17]. Horeweg and colleagues, analyzing the NELSON cohort, showed that volumetric growth assessment on repeat low-dose CT substantially improves discrimination over a single baseline scan, informing the two-scan protocols later adopted by several screening programs [18].

4. Functional imaging and the limits of PET-CT accuracy

FDG-PET adds metabolic information CT morphology cannot provide, and a landmark meta-analysis by Gould and colleagues pooling dozens of studies established sensitivity around 97% and specificity around 78% for

characterizing nodules and masses [19]. That aggregate accuracy is strongly modulated by nodule size and regional disease prevalence. Sensitivity falls sharply below approximately 8-10 mm because of partial-volume averaging and respiratory motion inherent to PET spatial resolution. Herder and colleagues showed that combining FDG-PET with a structured clinical model, rather than interpreting avidity alone, materially improves accuracy over either component [20].

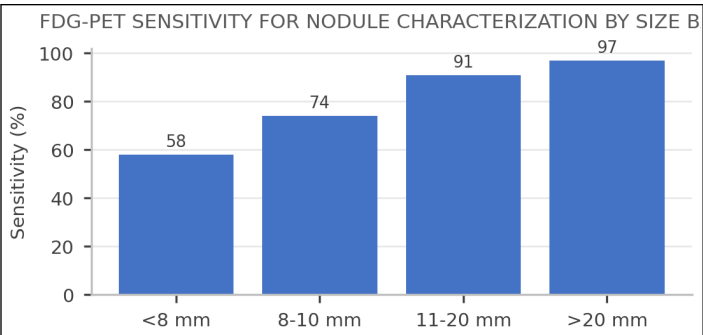


Figure 1: FDG-PET sensitivity for pulmonary nodule characterization by nodule size band, falling sharply below approximately 8-10 mm because of partial-volume averaging and respiratory motion, alongside the pooled sensitivity and specificity estimates from meta-analysis across mixed-prevalence populations [19,21].

Regional granulomatous disease prevalence is the other major modifier, degrading specificity rather than sensitivity. Deppen and colleagues' meta-analysis, restricted to regions with high endemic fungal or mycobacterial infection, found specificity substantially lower than mixed-prevalence estimates, because granulomas there are frequently metabolically active and generate false positives indistinguishable from malignancy [8]. Grogan and colleagues, analyzing PET accuracy within the prospective ACOSOG Z4031 surgical cohort, similarly found real-world performance fell short of meta-analytic pooled estimates, reinforcing that reported accuracy depends on population and prevalence context [21].

5. Structured clinical prediction models

Because no single feature reliably achieves adequate discrimination alone, structured multivariable models

combining patient and nodule predictors consistently outperform unstructured gestalt or size-threshold-only approaches. The Mayo model achieved an area under the receiver operating characteristic curve of roughly 0.80-0.83 across validation cohorts, establishing that a small set of readily available variables substantially outperforms intuitive estimation [2]. The Veterans Affairs model developed by Gurney and colleagues using Bayesian analysis offered a comparable, explicitly probabilistic framework, and later head-to-head validation against the Mayo model found neither consistently dominant across all nodule subtypes, underscoring that model choice should match the population applied [1].

Table 2: Major structured clinical prediction models for pulmonary nodule malignancy risk and their reported discrimination [2,1,12].			
Model	Population	Key variables	Reported AUC
Mayo Clinic (Swensen)	Incidental nodules	Age, smoking, prior cancer, diameter, spiculation, location	~0.80-0.83
Veterans Affairs (Gurney, Bayesian)	Incidental nodules	Clinical and radiographic variables, Bayesian weighting	Comparable to Mayo in head-to-head validation
Brock University (McWilliams)	Screening-detected nodules	Age, sex, family history, emphysema, size, count, spiculation, type, upper-lobe location	>0.90 in derivation and validation
Herder (clinical model + PET)	Indeterminate nodules referred for PET	Mayo model variables plus FDG-PET avidity	Improved over either component alone

The Brock model derived by McWilliams and colleagues from the Pan-Canadian cohort addressed the screening-detected population specifically, a group systematically different from the incidentally detected nodules underlying the Mayo model, achieving an area under the curve above 0.90 by incorporating nodule count, spiculation, type, and location alongside age, sex,

family history, and emphysema [12]. This population-specificity is itself a predictor of a model's own accuracy: a model validated in a screening population tends to overestimate risk when applied naively to an incidental-nodule population with different prevalence, which is why guideline documents from the American College of Chest Physicians and the British Thoracic Society recommend matching the model to clinical context rather than defaulting to a single calculator [22,23,11]. Herder and colleagues' demonstration that adding PET to a clinical model improves discrimination over either alone reinforces that combining independent predictive domains outperforms any single-domain approach [20].

6. Radiomics, deep learning, and quantitative image analysis

The most active area of current development addresses whether quantitative image analysis, beyond the handful of features a radiologist typically reports, can improve accuracy further than conventional interpretation and clinical models. Aerts and colleagues' foundational radiomics work showed that quantitative features extracted from CT, capturing intensity, shape, and texture not readily assessed by eye, carry phenotypic information correlated with underlying tumor biology [24]. Chae and colleagues applied this to persistent part-solid ground-glass nodules, showing computerized texture analysis distinguishes preinvasive from invasive adenocarcinoma better than visual assessment of the solid component alone, extending earlier texture-based computer-aided diagnosis work into a clinically actionable predictor [16].

Deep convolutional neural networks trained end-to-end on large datasets have since matched or exceeded the discrimination of radiomics pipelines and clinical models in retrospective validation. Ciompi and colleagues showed a deep-learning system could classify screening-detected nodules into clinically relevant subtypes with accuracy

approaching experienced radiologists [25]. Causey and colleagues combined deep and handcrafted radiomic features to achieve high malignancy-prediction accuracy on an independent dataset, showing hybrid approaches can outperform either alone [26]. Ardila and colleagues trained a three-dimensional model on National Lung Screening Trial data that matched or exceeded a radiologist panel on current and prior scans, with particular improvement in reducing false positives [27]. Baldwin and colleagues externally validated a convolutional neural network tool in an independent UK cohort with discrimination comparable to the Brock model, underscoring that a model's derivation-cohort accuracy routinely overstates external performance and that external validation is essential before deployment [28]. At the detection stage, Setio and colleagues' LUNA16 challenge established a standardized benchmark for automated nodule detection, an essential prerequisite for downstream characterization since detection sensitivity is itself an upstream predictor of overall pipeline accuracy [29].

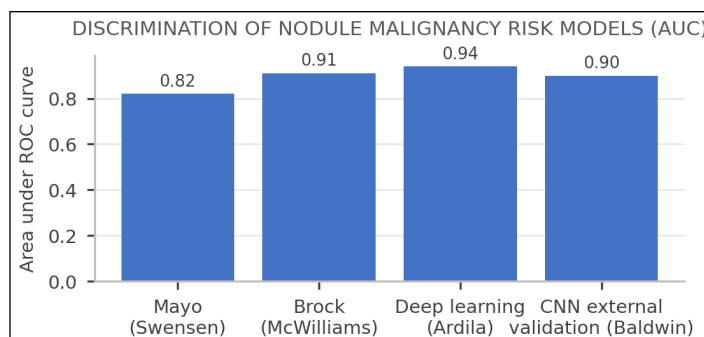


Figure 2: Discrimination, expressed as area under the receiver operating characteristic curve, for conventional clinical prediction models compared with radiomic and deep-learning approaches across their respective derivation and external validation cohorts [2,12,27,28].

7. Guideline-based integration of predictors into practice

Guideline bodies have progressively formalized these predictors into structured algorithms rather than individual judgment. The Fleischner Society's 2017 guidelines stratify management by size, consistency, and

patient risk category, operationalizing the predictors above into follow-up intervals balancing early detection against overinvestigation [10]. Lung-RADS applies a comparable size- and morphology-based scheme calibrated to the screening population's lower background malignancy rate and higher volume, distinct from the incidental-nodule context of the original Fleischner recommendations [30]. The American College of Chest Physicians and British Thoracic Society guidelines recommend applying a validated probability model rather than gestalt whenever feasible, and both incorporate PET-CT for solid nodules above a size threshold where sensitivity is reliable, directly reflecting the size-dependent PET limitation described above [23,11]. Winer-Muram's widely cited synthesis likewise frames diagnostic strategy as a stepwise integration of pretest probability, morphology, growth, and functional imaging rather than reliance on any single test [31].

8. Conclusion

Diagnostic accuracy in pulmonary nodule imaging is not a fixed property of any single test but the product of interacting predictors: pretest probability shaped by age, smoking history, and regional disease prevalence; size, morphology, consistency, and growth behavior on CT; the size- and prevalence-dependent performance of FDG-PET; population-matched structured prediction models; and increasingly, quantitative radiomic and deep-learning analysis [2,12,19,8,27]. No single predictor dominates across the full range of nodules encountered, which is why guideline bodies have converged on structured, multivariable approaches combining these predictors rather than defaulting to any one feature, threshold, or modality [10,11,23]. As radiomic and deep-learning tools mature toward externally validated, prospectively deployed clinical use, the practical challenge is less the discovery of new predictors and more the disciplined integration of those already established, matched to the population and clinical context in which a given nodule was found [28,29].

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