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Journal club

# Management of incidental nodules in lung cancer screening: ready for prime-time?

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## Commentary on:

Silvestri GA, *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: 491–500.

## Context

Lung cancer is the leading cause of cancer-related mortality. Two independent trials from the USA and the Netherlands and Belgium demonstrated that annual low-dose computed tomography (LDCT) screening reduced mortality by 20% and 26%, respectively [1–3]. LDCT is therefore widely accepted as the preferred method for detecting pulmonary nodules, but raises an important clinical challenge concerning nodule evaluation and patient management [4–7]. Current pulmonary nodule evaluation and clinical management starts by estimating the probability of cancer (pCA) based on clinical (age, symptoms, smoking history, performance status, associated lung diseases, family history and previous clinical history) and radiological (size, growth and morphology) parameters, and takes into account the patient's preferences. Certain lung nodule features suggest a high likelihood of malignancy (such as spiculation, lobulation and pleural retraction) whereas others favour a benign aetiology (internal fat, calcifications and round shape) [8–10]. Furthermore, the likelihood of malignancy and nodule diameter are positively correlated. However, nodule size is not a reliable standalone malignancy biomarker as slow growing adenocarcinoma nodules will appear small, and benign lesions may show growth and volume doubling time in the range of malignant nodules [11]. Hence, the assessment of pulmonary nodules remains a diagnostic challenge. Cohorts with low to moderate malignancy risk lung nodules pose the clinical dilemma between invasive procedures and serial surveillance. A score that could reliably predict pulmonary nodule aetiology would improve patient management by minimising the number of invasive procedures and reducing healthcare costs and patients' discomfort [12]. To this end, patients with a probably benign nodule could be managed by serial surveillance avoiding invasive tests, whereas those patients with a probably malignant nodule could be stratified to the most appropriate treatment more quickly [13]. These authors previously developed a biomarker-driven lung nodule classifier based upon 222 subjects [14]. In this study, Silvestri *et al*. [15]. designed and implemented a multicentre, double-blinded, prospective, observational study with a retrospective evaluation to validate the accuracy of this lung nodule classifier.



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**Current clinical management of lung nodule patients is inefficient and therefore causes patient misclassification, which increases healthcare expenses. A precise and robust lung nodule classifier could minimise healthcare costs and discomfort for patients.** http://bit.ly/2oMIEwQ

# Methods

## Study subjects

The trial included subjects over 40 years old with incidental lung nodules 8–30 mm in diameter and a clinician-assessed pCA ≤50%. All subjects were recruited within 60 days after the baseline CT scan that detected the nodules. Exclusion criteria included detection of the nodule by a previous CT/positron emission tomography (PET) scan, previous biopsy of the nodule, positive cancer diagnosis within 2 years, and transfusion of blood products within 30 days of enrolment.

## Data collection

The researchers collected the following clinical and radiological data at baseline and follow-up time points: subjects' demographic data, CT images, pCA, clinical characteristics of the nodules and blood samples. Lung nodules were characterised as benign after histopathological diagnosis, radiographic resolution or no growth in the year after presentation. Cancer diagnosis was based on histopathological criteria.

## Integrated nodule classifier

Proteomic analysis of two plasma proteins, LG3BP and C163A, was performed by multiple reaction monitoring mass spectrometry (MS). LG3BP was found to be elevated in cancer patients' serum and might play a role in the immune response. C163A is linked to the clearance and endocytosis of haemoglobin/haptoglobin complexes by macrophages The classifier is built to yield a post-test probability of benignity. It is based on the abundance of plasma proteins LG3BP and C163A, combined with five clinical risk factors: age (years), smoking status (never, former, current), nodule diameter (largest nodule in mm), edge characteristics (smooth, spiculated, lobulated), and location.

## Performance assessment and potential impact

The performance of the classifier was evaluated by its sensitivity, specificity, area under the receiver operating characteristic curve (AUCROC) and positive (PPV) and negative predictive value (NPV) metrics. The classifier performance was compared to the physician's assessment, clinical prediction models and a PET scan. Moreover, the authors assessed the clinical impact of the classifier by estimating the potential reduction of invasive procedures, if the classifier results were known.

# Main results

Out of 685 participants enrolled in the study, 178 were finally eligible for analysis (figure 1). Cancer prevalence for the eligible group was 16%. Benign lung nodules were found to be smaller and the pCA increased with increasing nodule size. The referrals for PET, biopsies and surgery had a positive correlation with pCA, whereas serial imaging and pCA were negatively correlated. The performance analysis of the classifier showed a sensitivity of 97% (CI 82%–100%), a specificity of 44% (CI 36%–52%) and a post-test probability of 98% (CI 92%–100%) in distinguishing benign from malignant nodules. The performance of the classifier was superior compared with physician's pCA estimates, PET scan, and Veterans Affairs and Mayo models as evaluated by the McNemar test and AUCROC. The classifier exhibited a potential to reduce invasive procedures, since there would have been 40% fewer procedures in patients with benign nodules. However, 3% of the malignant nodules would also have been mislabelled, delaying their appropriate management.

# Commentary

Overall, lung cancer detection can be improved by: 1) refining the screening selection criteria;

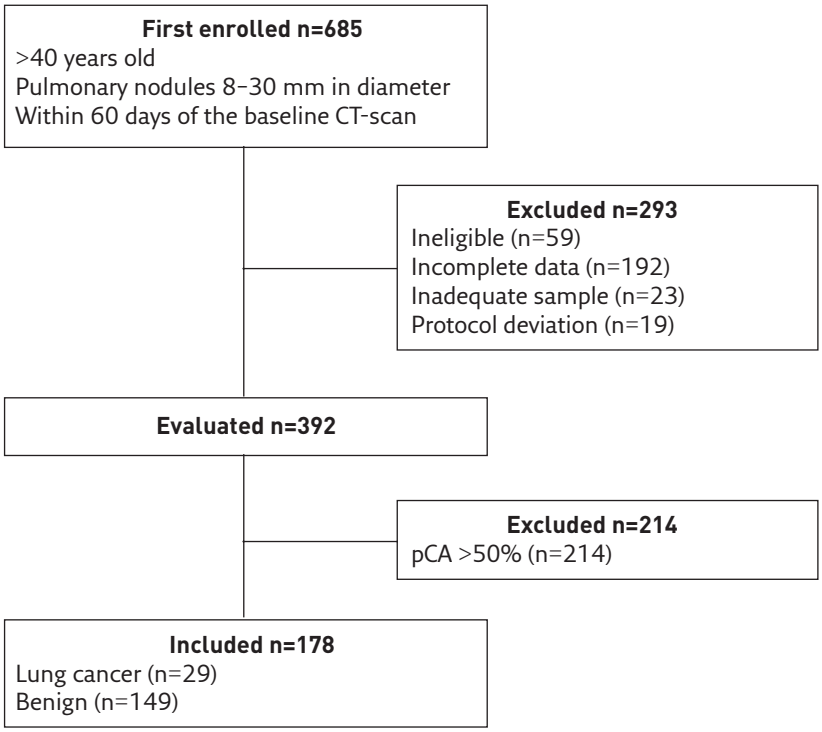


**Figure 1** *Out of 685 subjects included in the study 507 were excluded from the analysis due to ineligibility (n=59), incomplete clinical data (n=192), protocol deviations (n=19), serum samples not appropriate for analysis (n=23) or pre-test probability of malignancy over 50% (n=214). 178 subjects were eligible for analysis.*

2) developing computer-aided (artificial intelligence) diagnosis methods to make chest CT interpretation easier; 3) developing biomarkers to detect early-stage lung cancer and/or classify lung nodules; and 4) using highly sensitive bronchoscopic techniques to enhance the detection rate of central airway lesions. This study focusses on the third option and is the largest prospective trial to assess the accuracy of a biomarker-driven classifier for lung nodule evaluation. While patients with low cancer risk nodules (pCA <5%) are managed with serial CTs and high cancer risk patients (pCA >65%) with surgery, there remains a grey zone of moderate cancer risk patients (5%<pCA<65%) wherein diagnosis and management are more clinically challenging. The classifier demonstrated promising results as rule-out test when evaluated in the moderate cancer risk cohort. Recently, deep learning chest imaging diagnosis was found to outperform radiologists with an AUCROC of 94% [16].

In the setting of early lung cancer diagnosis, blood is an evident first choice to look for biomarker candidates. Blood-based biomarkers provide an overview of the patient's whole body, including the primary tumour, metastatic disease, immune response and peritumoural stroma. MS has evolved as a powerful technology for protein detection and quantification in complex samples such as plasma. However, MS assays quantify the average amount of peptides and proteins, as subcellular localisation of protein expression is not possible without additional sample processing such as macro- or micro-dissection. Furthermore, some proteins and post-translational modifications may remain below the lower threshold of quantification. Targeted MS assays, which are now beginning to be implemented in clinical laboratories and clinical trials, can overcome these issues. A panel of inflammation biomarkers could be useful for lung cancer detection since inflammation is a hallmark of cancer [17]. However, lung cancer patients frequently have additional inflammatory comorbidities, like COPD, that elevate baseline levels and therefore make the discrimination between benign and malignant lung nodules more difficult [18]. The complexity of lung cancer pinpoints the need to take comorbidities into account when designing biomarker discovery studies [19].

In addition to blood, other specimens are available for biomarker searches, including sputum, bronchial lavage, exhaled breath and airway epithelium aspirate samples [20]. These can provide information regarding molecular changes to tissues that are anatomically closer to the tumour cells and their microenvironment, and therefore, potentially more relevant and accurate for clinical decision making. The LuCID (Lung Cancer Indicator Detector, clinicaltrials.gov: NCT02612532) trial was designed to evaluate the combination of exhaled breath and machine learning techniques for early stage lung cancer detection in patients at risk, and its results are expected soon.

The strengths of the study by SILVESTRI *et al*. [15] lies in its robust design, including the in-depth description of the standard operating procedures, a double-blinded protocol and the use of two independent datasets to develop and validate the classifier. Moreover, the authors used a state-of-the-art high precision and high specificity multiple reaction MS assay to screen the plasma samples.

Nonetheless, the authors chose to determine nodule stability at 1 year follow-up despite the international clinical guidelines suggesting 2 years of evidence of no growth. Moreover, the analysis was carried out retrospectively, and thus, a prospective trial is required to evaluate the clinical utility of the classifier, monitoring changes in practice. Follow-up CT scans are missing for 88 patients and the practices between different clinical units are under-represented.

## Implications for practice

The authors evaluated clinical validity of the nodule classifier and suggest that it could lead to 40% fewer invasive procedures for subjects with pCA <50%. This is important since current clinical classification algorithms are inefficient and 43% of lung biopsies turn out to be benign. To this end, the use of this classifier could minimise healthcare costs and discomfort for patients. Also, the psychological impact on patients is an aspect that needs more attention [21]. According to FREIMAN *et al.* [22], 25% of patients experience clinically significant nodule-related distress, directly influencing patients' quality of life. The classifier needs optimisation, as this study suggests that 3% of the cancer patients might be missed. Future studies could add deep learning techniques alongside biomarker discovery to develop more accurate and robust prediction models. Furthermore, an enriched classifier could provide a personalised timeframe for follow-up screenings for early-stage lung cancer survivors and low pCA subjects and predict the outcome and response to adjuvant therapy for those at high-risk of recurrence [23].

In conclusion, this study evaluated the efficiency of a prognostic score tailored to stratify lung nodule patients. Although promising, further assessment of the prognostic score's clinical utility regarding the potential benefit or harm for patients is required. Towards the era of personalised medicine, this PANOPTIC score holds promise for optimising patient management, rendering screening to be more cost-effective, avoiding unnecessary procedures and relieving patients' distress.

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## Support statement

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## Conflict of interest

N. I. Kanellakis has nothing to disclose. K. Lamote reports grants from Kom op tegen Kanker (Stand up to Cancer), the Flemish cancer society, during the conduct of the study.

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