Editorial

Editorial on PanCan study

Henry M. Marshall, Ian A. Yang, Rayleen V. Bowman, Kwun M. Fong

Thoracic Research Centre, University of Queensland, The Prince Charles Hospital, Brisbane, Australia

Correspondence to: Henry M. Marshall, PhD, FRACP. Thoracic Research Centre, University of Queensland, The Prince Charles Hospital, Rode Road, Brisbane 4032 QLD, Australia. Email: Henry.marshall@health.qld.gov.au.

Provenance: This is an invited Editorial commissioned by Section Editor Dawei Yang (Zhongshan Hospital, Fudan University, Shanghai Respiratory Research Institution, Chinese Alliance Against Lung Cancer, Shanghai, China).

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Lung cancer accounts for an estimated 1.4 million deaths per year globally. The combination of primary prevention, aimed at reducing tobacco consumption, and screening, aimed at detecting early-stage tumours offer significant opportunities to reduce the burden of this disease. Although tobacco control policies are proven and cost-effective, screening has yet to earn its place in routine care outside of the United States. The seminal National Lung Screening Trial (NLST) demonstrated that screening could achieve 20% relative mortality reduction compared to usual care (screening with plain chest radiograph) (1). NLST eligibility was based on a very simple, bivariable risk assessment consisting of age (55 to 74 years) and smoking history (30 pack-year smoking history and current smoker or had quit within the prior 15 years). The Cancer Intervention and Surveillance Modeling Network (CISNET) confirmed the NLST eligibility criteria were most likely to be effective and subsequent positive recommendations from the US Preventive Services Task Force (USPSTF) and Centers for Medicare and Medicaid Services enabled roll-out of screening the US based on slightly modified age criteria (persons 55–80 or 77 years of age). However, the high rate of false-positive scans and attendant work-up coupled with uncertain cost-effectiveness has stalled screening roll-out in other countries, many of whom are conducting their own screening pilot programs or waiting for confirmatory results from the NELSON trial or pooled European data. The question has been raised: are we targeting the highest-risk population?

Efforts to better-define the target population are ongoing. The premise being that most detectable lung cancers are harboured in highest-risk individuals and that multivariable risk assessment using a regression model will provide a more sensitive and specific estimate of risk than bivariable risk assessment as per NLST. In turn, a more accurate screening program should be more cost-effective.

Many risk estimation models have been published. Retrospective validation against screening trial data support their superiority over standard eligibility criteria, including NLST and USPSTF (2-5) and, in the absence of formal cost-effectiveness analysis, greater Net Benefit using decision curve analysis (6). The PLCOm2012 model (3), developed using data from the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, is arguably the most accurate model.

Although retrospective validation studies look promising, the lack of prospective validation studies represents an important evidence gap. Now, two groups have reported prospective risk model validation, UKLS and PanCan (7). Published in 2016, the UKLS pilot study estimated risk using LLPv2 model at an eligibility threshold of 5% over a 5-year horizon. One-year follow-up data are encouraging: baseline lung cancer prevalence and stage shift was better than NLST (1.7% prevalence, 85.7% stage I or II respectively in UKLS compared 1.1% and 61.6% respectively in NLST after 1 year) (8,9).

The PanCan group, take this further by reporting long-term data (7)—a median follow-up of 5.5 years using a model which estimated risk over a 6-year horizon. The PanCan model, a version of PLCOm2009 (10),

and forerunner of PLCOm2012 (3), used eight easily obtainable clinical variables: age (four ordinal levels), education (dichotomous; beyond high school *vs*. high school completion, and less); family history of lung cancer (no *vs*. yes); body-mass index (dichotomous at 30 kg/m^2 or greater); chest X-ray in last 3 years (ordinal as 0, 1, and on more than one occasion); chronic obstructive pulmonary disease (COPD) history (no *vs*. yes); smoking duration (years); pack-years smoked. Individuals were eligible for screening if their risk of lung cancer was ≥2% over 6 years. The PanCan cohort appears typical for screening trials but differed from NLST in some of the key risk factors, e.g., higher median age (62 *vs*. 60 years); substantially more current smokers (62% *vs*. 48%); higher median pack years (50–53 *vs*. 48) but fewer males (55% *vs*. 59%).

The primary outcome of the study was lung cancer incidence. After a median follow-up of 5.5 years the cumulative incidence and incidence rates per 10,000 person-years follow-up were significantly higher than the NLST [6.5% and 138 per 10,000 person-years *vs*. 4·0% and 64 respectively (1)]. The secondary outcome was stage distribution. PanCan detected a higher proportion of stage I/II cancers than NLST (77% *vs*. 57.1%, P<0.0001).

A total of 136 (79.5%) of cancers were detected at baseline (T0), and 17 at T4, whereas in NLST the numbers of cancers was more evenly distributed across screening time-points. Participant retention was 70% at T4, which might explain the lower incidence of lung cancer observed later in the trial; however, over-diagnosis may also be a factor. The interval cancers in PanCan were generally higher stage than screen detected cancers as expected in a screening trial. As the authors point out, differences between trials such population characteristics and study methods, as well as selection criteria, may contribute towards the higher observed prevalence and incidence of lung cancer.

Both the UKLS and PanCan are supported by economic analysis and appear cost-effective (8,11,12), reporting incremental cost effectiveness ratios (ICER) per quality-adjusted life-year (QALY) gained well under respective national cost effectiveness (CE) thresholds (GBP 8,466 per QALY for screen detected *vs*. symptomatic cases, CE threshold GBP 20,000; and CAD 20,724 per QALY for screening *vs*. no screening, CE threshold CAD100,000). In contrast, NLST CE analysis (13) estimated a much higher ICER of USD 81,000 per QALY for screening *vs*. no screening, although this is still within the US CE threshold of USD 100,000. Interestingly, NLST noted a greater than threefold difference in cost per QALY in the lowest risk quintile compared to the highest risk quintile when stratified using the PLCOm2012 risk model.

Notably, the authors do not explain the rationale behind the choice of 2% risk threshold (the optimal PLCOm2012 threshold has been determined to be 1.51% for example), and importantly, this paper cannot tell us the proportion of participants who did not meet the threshold that went on to develop lung cancer. This is relevant because the PanCan model underestimated the observed risk of lung cancer by 30% in the cohort and the non-enrolled group still had significant smoking exposures, albeit lower than the enrolled group (e.g., mean pack-year smoking exposure was 38 pack years in non-enrolees). Evidence-based selection of threshold is paramount as it represents a trade-off between sensitivity and specificity and may need to be adjusted to suit the population and health care setting.

So, which model to use? Prior studies have found little to choose between various risk models, although the PLCOm2012 does appear to have a slight advantage, at least statistically. The PanCan authors compared the statistical accuracy of the PanCan and PLCOm2012 models. PLCOm2012 uses 11 variables and differs from the PanCan model in these respects: family history of lung cancer, history of COPD and smoking duration remain the same; age and body mass index (BMI) were changed to continuous data; education was stratified to six ordinal levels; five new variables (ethnicity, personal history of cancer, smoking status, cigarettes per day and smoking quit time) were added; and two variables (pack-years and chest X-ray in past 3 years) were removed. Although the PanCan trial was not powered to detect differences in model performance, discrimination [receiver operating characteristic (ROC) area under the curve (AUC)] and calibration were not statistically different between models. The PLCOm2012 model is itself being prospectively tested in the International Lung Screening Trial along with nodule multivariable risk assessment to guide downstream management.

Thus, the evidence to refine screening methods continues to evolve. Selection of the optimal target population to screen is fundamentally important in delivering cost-effective screening and the PanCan team must be congratulated on producing important new evidence that multivariable risk estimation is the tool of choice.

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Footnote

Conflicts of Interest: the authors are all co-investigators in the International Lung Screening Trial (ILST).

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