Editorial on PanCan for Translational Lung Cancer Research

**Title:**

**Patient selection for future lung cancer CT screening programmes: lessons learnt post NLST.**

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Successful implementation of low radiation dose CT lung cancer screening, depends on a number of well-researched factors that improve the balance between benefits and harms. One of the most important is the identification of individuals at high risk of developing and dying from lung cancer. There is debate about the threshold that defines high enough risk and the method for estimating risk, with several multivariable risk models available. The findings from the PanCan study shed further light on this topic.

Although there is still debate about whether LDCT lung cancer screening should be offered at all, most protagonists agree that screening should only be offered to people with a high risk of lung cancer, where benefits are likely to outweigh harms and the number needed to screen to prevent a death supports cost effectiveness. Since the publication of the National Lung Cancer Screening Trial (NLST ) [1] which demonstrated that lung cancer screening can reduce mortality by 20% in high risk smokers, it has been shown that the number needed to screen was lowest in the 40% of recruits who were at highest risk [2]. Accordingly, cost effectiveness was also highest in the high-risk groups [3]. The US Preventive Forces Task Force recommended that lung cancer screening was based on age –extended NLST selection criteria [4] (55 – 80 years of age, minimum 30 pack years and quit smoking within the previous 15 years).

A number of publications have shown that lung cancer risk prediction models out-perform these criteria, both increasing the sensitivity for identifying those who develop lung cancer and reducing the number screened who do not develop cancer. One of the first risk models used in a lung cancer CT screening project setting, was the PanCan risk model [5], which predates the $PLCO_{m2012}$ [6]. PanCan was utilised in the Pan-Canadian early detection study, started in 2004, undertaken in eight centres in Canada and the recruited participants were offered three consecutive scans. PanCan was a cohort study and the patients' were not recruited at random but through advertising campaigns. PanCan selected the participants on the basis of their model predicted risk (2% over 6 years) and 2537 patients were recruited and received a baseline screen.

Since this study was started, 14 years ago, radiological protocols for CT screen detected nodules have been improved based on accumulating evidence, including that from the PanCan study [7]. PanCan defined an abnormal CT as the presence of any non-calcified or non-perifissural pulmonary nodule of at least 1 mm maximum diameter [5]. The NLST trial

used 4mm maximum diameter as their threshold, whilst the NELSON and UKLS utilised volumetric analysis [8] [9]. The current volumetric management of screen-detected pulmonary nodules is outlined in the recent European Union Position Statement (EUPS) [10].

Based on modelling, the PanCan investigators calculated that the median risk in the population screened was 3.3% but found that the incidence of lung cancer over 5.5 years was double that (6.5%, 164/2537) which is also significantly higher than that reported by the NLST, with a 4% incidence. The PanCan and $PLCO_{m2012}$ risk models demonstrated, at best, modest overall prediction with ROC AUC‡ of 0·629 (95% CI 0·588-0·667) and 0·614 (95% CI 0·570-0·658) respectively, (data only shown in the supplementary PanCan publication[5]).

PanCan has provided convincing evidence of a non RCT study utilising a risk prediction model with 5.5 years of follow-up. $PLCOm_{2012}$ has been shown to outperform the NLST entry criteria, which are similar to the USPSTF criteria (apart from age criteria 55-80y) upon which reimbursement is based in North America. However, the disparity in the PanCan baseline detection 5.1% rate of lung cancer (129 individuals with cancer, of 2537 screened), with estimated average risk and the modest AUC, show that there is room for improvement, something that has also been demonstrated in modelling studies [11]. UKLS, the only published RCT to use a risk prediction model to select subjects utilised a 5% risk over 5 years [9], yet the baseline detection rate was lower at 2.1%, and much more in keeping with what would be expected after a single screen. UKLS has not yet published the 5 year cumulative cancer incidence but this potentially could now be measured to confirm the predictive accuracy of the $LLP_{v2}$ model.

There have only been two major lung cancer screening projects undertaken in North America since the publication of the NLST. The PanCan trial can be compared in a number of ways with the CT lung cancer demonstration project undertaken by the US Veterans Affairs (VA) health system lung cancer screening programme, which started in 2015[12]. The VA lung cancer screening project utilised the USPSTF recommendations, surprisingly, this project had a very high rate of false positives with 56% of the 2184 subjects screened, (i.e. nodules requiring follow up with repeat scans or invasive procedures), compared with the NLST 26.3% [1, 12] . Lung cancer was detected in 1.5% and the low rate of detection of early stage disease is disappointing. Indeed, this is in sharp contrast to many other studies, including the most recent real-world demonstration programmes in Manchester UK, which utilised the

$PLCO_{m2012}$ risk prediction model [13] and the Liverpool Health Lung Project , utilising the $LLP_{v2}$ risk model [14], to select high risk patients . This has naturally raised the question if a more targeted approach had been used, would the VA project have been more successful; which has been addressed by Caverly and colleagues [15]. Firstly, they used previously published findings from NLST that the 20% relative risk reduction in lung cancer mortality did not change according to baseline risk. Thus, they calculated absolute risk reduction and utilised the Bach risk model to calculate the annual baseline mortality risk and analysed the data by risk quintiles. It's of note that Caverly et al. used the Bach lung cancer risk model [16], which is considered one of the simplest models but has been shown to perform similarly, when compared to the more complex models [11] . The Bach model only utilises smoking and age. Unsurprisingly, the patients in the higher quintiles in the VA project had a significantly larger number of cancers (number of lung cancers diagnosed / 1000 screened; quintile 1, 4.8 v 29.7 in quintile 5). The number required to screen / lung cancer death prevented: 6903 in quintile 1 compared with 687 in quintile 5. However, the false positive rate did not change greatly across the quintiles.

Both the PanCan and the re-analysed VA study utilising the Bach risk model reflect the use of participant selection and nodule management protocols, the latter is now considered outdated, partly as a result of data generated by the PanCan study and the models are clearly suboptimal. Given the marked influence of accurate risk prediction on the cost effectiveness of CT screening, itself a balance of resource utilisation and minimisation of harms, it is essential that more work is devoted to the development on models and the method of participant recruitment in the real world. Selection of a high-risk group using $PLCO_{m2012}$ has been successful in Manchester, but it is unclear how much the model influenced the excellent results, as the vast majority of patients were clearly at high risk and a model would not have been required to select them. Indeed, models are only really useful in determining eligibility where it is close to the agreed risk threshold. Developing models specifically designed to address this subgroup may be a future approach. The EUPS on lung cancer screening [10] demonstrates the dramatic leap in our understanding around patient selection and nodule management, thus resetting the balance between harm and benefit in the patient favour as, well as reducing false positive rates. The EUPS recommends that either of the two risk models $PLCO_{m2012}$ and the $LLP_{v2}$ could be utilised at this time, although refinement of models is important. Risk thresholds will be mainly dependent on the cost acceptable in each country (i.e. utilising the LLPv2 at 3% risk will increase the number of cancer identified but

will require a significantly larger number of patients to be screened [17]). This is clearly seen in the cost effectiveness studies undertaken in the PanCan, NLST and UKLS CT screening projects, CAN$20,724 per life gained [18], the NLST with US$81,000 [3] and the UKLS £6,325 per life-year gained [9].

Countries implementing future lung cancer screening programmes, will have to decide on the most appropriate risk assessment model and threshold, to select their high-risk individuals, based on their national health funding model (insurance or public purse), the level of acceptable cost effectiveness, together with the social and ethical attitudes to screening, based on 'personal risk factors'. To date we have little information on the latter.


1. National Lung Screening Trial Research T, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD: **Reduced lung-cancer mortality with low-dose computed tomographic screening.** *N Engl J Med* 2011, **365:**395-409.
2. Katki HA, Kovalchik SA, Berg CD, Cheung LC, Chaturvedi AK: **Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening.** *JAMA* 2016.
3. Black WC, Gareen IF, Soneji SS, Sicks JD, Keeler EB, Aberle DR, Naeim A, Church TR, Silvestri GA, Gorelick J, et al: **Cost-effectiveness of CT screening in the National Lung Screening Trial.** *N Engl J Med* 2014, **371:**1793-1802.
4. **USPSTF Lung Cancer Screening** [http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lung-cancer-screening]
5. Tammemagi MC, Schmidt H, Martel S, McWilliams A, Goffin JR, Johnston MR, Nicholas G, Tremblay A, Bhatia R, Liu G, et al: **Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study.** *Lancet Oncol* 2017, **18:**1523-1531.
6. Tammemagi CM, Pinsky PF, Caporaso NE, Kvale PA, Hocking WG, Church TR, Riley TL, Commins J, Oken MM, Berg CD, Prorok PC: **Lung cancer risk prediction: prostate, lung, colorectal and ovarian cancer screening trial models and validation.** *J Natl Cancer Inst* 2011, **103:**1058-1068.
7. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, Yasufuku K, Martel S, Laberge F, Gingras M, et al: **Probability of cancer in pulmonary nodules detected on first screening CT.** *N Engl J Med* 2013, **369:**910-919.
8. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, van Iersel CA, van den Bergh KA, van 't Westeinde S, van der Aalst C, et al: **Management of lung nodules detected by volume CT scanning.** *N Engl J Med* 2009, **361:**2221-2229.
9. Field JK, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T, Green BA, Holemans JA, Kavanagh T, Kerr KM, et al: **The UK Lung Cancer Screening Trial: a pilot randomised**

**controlled trial of low-dose computed tomography screening for the early detection of lung cancer.** *Health Technol Assess* 2016, **20:**1-146.
10. Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch HH, CP. Bastarrika, G. Sverzellati , N. Mascalchi , M. Delorme, S. Baldwin, DR. Callister, ME. Becker, N. Heuvelmans, MA. Rzyman, W. Infante, MV. Pastorino, U. Pedersen, JH. Paci, E. Duffy, SW. de Koning, H. Field, JK.: **EU Position Statement on Lung cancer Screening.** *Lancet Oncology* 2017, **12.:**e754-e766. .
11. Ten Haaf K, Jeon J, Tammemagi MC, Han SS, Kong CY, Plevritis SK, Feuer EJ, de Koning HJ, Steyerberg EW, Meza R: **Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study.** *PLoS Med* 2017, **14:**e1002277.
12. Kinsinger LS, Anderson C, Kim J, Larson M, Chan SH, King HA, Rice KL, Slatore CG, Tanner NT, Pittman K, et al: **Implementation of Lung Cancer Screening in the Veterans Health Administration.** *JAMA Intern Med* 2017, **177:**399-406.
13. Crosbie PA, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D, Duerden R, Eaglesfield J, Edwards T, Elton P, et al: **Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester.** *Thorax* 2018.
14. **Liverpool Health Lung Project Interim Report 2017** [http://www.liverpoolccg.nhs.uk/health-and-services/healthy-lungs/]
15. Caverly TJ, Fagerlin A, Wiener RS, Slatore CG, Tanner NT, Yun S, Hayward R: **Comparison of Observed Harms and Expected Mortality Benefit for Persons in the Veterans Health Affairs Lung Cancer Screening Demonstration Project.** *JAMA Intern Med* 2018.
16. Bach PB, Kattan MW, Thornquist MD, Kris MG, Tate RC, Barnett MJ, Hsieh LJ, Begg CB: **Variations in lung cancer risk among smokers.** *J Natl Cancer Inst* 2003, **95:**470-478.
17. K. Ten Haaf, H. De Koning, Field JK: **Selecting the Risk Cut off for the LLP Model.** *Journal of Thoracic Oncology* 2017, **12:**S2174.
18. Cressman S, Peacock SJ, Tammemagi MC, Evans WK, Leighl NB, Goffin JR, Tremblay A, Liu G, Manos D, MacEachern P, et al: **The Cost-Effectiveness of High-Risk Lung Cancer Screening and Drivers of Program Efficiency.** *J Thorac Oncol* 2017, **12:**1210-1222.

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