Targeted screening for lung cancer is here but who do we target and how?

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In October 2019, an Independent Review of Adult Screening Programmes in England was published, authored by Mike Richards.[1] Two key recommendations were that targeted screening programmes should be given equal weight to population screening programmes and that there should be a single advisory body covering both population and targeted screening programmes. The review identified the importance of defining individual risk of cancer to identify a target population at sufficient risk of the condition to be cost-effective. Secretary of State for Health and Social Care, Matt Hancock has asked the chief medical officers of the four UK countries to agree a mechanism for overseeing the new 'targeted programmes'.[2] Screening for lung cancer with low radiation dose CT (LDCT) is the largest of these programmes and is a considerable challenge to implement. In other countries the distinction between population and targeted screening is emphasised less but the criteria used to select eligible people remain crucial in determining cost-effectiveness.[3 4] Targeting avoids subjecting people at low risk, who have little chance of developing the disease and benefiting from screening, to similar harms as those who are more likely to develop the disease and potentially benefit. Multivariable models have been shown to have better sensitivity and specificity than selection based on age and tobacco smoking alone, the most common criteria currently used on a global basis.[5 6] In the UK, the first trial to use a multivariable model to define eligibility was the UK Lung Screening Trial (UKLS).[7] The cancer detection rate was 2.1%, but there was some concern that the threshold risk (5% over 5 years) was too high.[8] UK pilots have used both the Liverpool Lung Project version 2 (LLP_{v2}), as was used in UKLS, and the Prostate Lung Colorectal and Ovarian (modified 2012) ($PLCO_{m2012}$), an earlier version of which was used to select subjects for the Pan-Canadian Early Detection of Lung Cancer (PanCan) study. The UK pilots found baseline cancer rates of 2%–3% and the PanCan study 5%.[9] For these reasons, the National Health Service England (NHSE) Lung Health Check targeted screening programme uses either a $PLCO_{m2012}$ 6-year risk-threshold of 1.51% and/or an LLP_{v2} 5-year risk-threshold of 2.5% to define eligibility, favouring this approach over the simple age and smoking criteria used in both the National Lung Screen Trial (NLST) and the Dutch–Belgian lung-cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON)).[10 11]

Lebrett *et al*[12] report on the performance of the two models ($PLCO_{m2012}$ and LLP_{v2}) in the Manchester pilot. They invited ever-smokers aged 55–75 years identified via electronic records of 14 participating general practices to a Lung Health Check and were able to assess the proportion of attendees eligible for screening, although only those meeting the $PLCO_{m2012}$ threshold of 1.51% (1429 persons) were invited for an LDCT. Cancer outcomes were only determined in those who had screening with LDCT; in total, 62 individuals were diagnosed with lung cancer. They found that the risk models selected the same number (56%) of attendees from the Lung Health Check population (LLP_{v2} 2.5% and $PLCO_{m2012}$ 1.51% threshold), whereas NLST criteria would have selected fewer people (47%). Among the 62 persons diagnosed with lung cancer, a strict application of the NLST criteria would have selected 51 of these individuals (82.3%). Applying the LLP_{v2} with a 5.0% threshold would have selected 46 (74.2%) for screening; while applying the 2.5% threshold would have selected 58 (93.5%) of these individuals. However, had LLP_{v2}, been used instead of $PLCO_{m2012}$, 272 people would have been selected for which the cancer outcomes are unknown. These individuals were older but with less tobacco use; a 1.5% cancer detection rate in these individuals (a further four individuals with cancer) would make the cancer detection rate the same for both models. Similarly, the cancer outcomes for the 94 persons eligible by the NLST criteria, but ineligible by the $PLCO_{m2012}$ criteria are unknown. However, given that within the Lung Health Check population 51 individuals with cancer were selected by the NLST criteria, at least 11 cancers would have to occur in these 94 individuals (ie, a 11.7% cancer rate) to match the 1.5% detection rate. The authors suggest that the $PLCO_{m2012}$ may underestimate the risk in a deprived population and that prospective evaluation is required. Such an evaluation is the primary outcome of the Yorkshire Lung Screening Trial. Lebrett *et al* also show that and LLP_{v2} threshold of 5% is almost certainly too high, so the lower threshold adopted by the NHSE programme is supported by the outcomes of their study.

A number of studies have compared multivariable models in mainly US data and have shown the $PLCO_{m2012}$ to one of the better ones in terms of discrimination and calibration.[5] Both performance measures can be influenced by the characteristics of a population so it is important that such evaluations are done across different countries. A number of other models may be simpler and more pragmatic, employing fewer variables but at the risk of excluding a group of people at higher risk.[13 14] LLP_{v2} is one of few models to include asbestos exposure, for example.[15] Perhaps more important is how models predict benefit from early detection. Most assessments of the long-term effects of LDCT screening to date use microsimulation models and natural history to identify the most efficient screening regimen. These models include predicted risk of lung cancer, corresponding lung cancer mortality and the individual's life expectancy in the presence and absence of screening in order to simulate an individual's entire life history, accounting for lifetime variations in lung cancer and smoking-related mortality risk.[16 17] However, there is a lack of real-world data on extent of morbidity and competing causes of mortality in populations selected by multivariable models. The Lebrett study has also confirmed previous observations that multivariable models select participants with considerable and potentially important comorbidity. This underlines that when selection models are applied, one should be careful not to base eligibility solely on an individual's risk for developing the disease, but also their potential benefit and risk for potential harms. On the positive side there is also a potential to detect and treat early other diseases that may be competing causes of death, predominantly ischaemic heart disease and chronic obstructive pulmonary disease . Future models might be able to include the detection of untreated heart and lung disease in their overall

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assessment of eligibility. This is complex but a worthy area for future research. The Risk Or Benefit IN Screening for CArdiovascular Diseases trial is currently looking at whether screening for cardiovascular disease, followed by preventive treatment is effective in reducing morbidity and mortality from coronary heart disease.[18]

Another consideration is that once enrolled into a programme, should further models be used to inform decision making on the optimal screening regimen, given a person's current characteristics and screening history?[19] The findings on the CT, development of new comorbidities and advancing age are all factors that may alter risk/benefit ratio and so determine if screening should continue or at least if the screen interval be extended. The NHSE programme used data from both NLST[20] and NELSON[21] to recommend a 24-month interval if no significant nodules were found at the prevalence screen, given that the initial funding was limited to two screens. More sophisticated approaches will be developed and tested in ongoing research.

On a pragmatic level, the emphasis in invitation for screening should be on cost effectiveness and total impact. These are largely determined by the proportion of invited people that benefit from the programme and the proportion of the general population that develops lung cancer that is invited. However, increasing the latter would require lowering the risk-threshold for screening eligibility. While this would increase the sensitivity of the invitation process, it will also inadvertently select more individuals at lower risk for whom screening is not beneficial or only causes harm (ie, a reduction in the specificity of the invitation process). The crux of an effective model is in balancing this trade-off between efficiency and total impact. The method of deployment of the models should also maximise participation rate which is crucial to maximise impact. In the UK, primary care data that include smoking history allow the approach illustrated by the Manchester team and that adopted in the Lung Health Check. Choosing ever smokers immediately includes the majority of people with lung cancer in the age range, approximately 50%. In countries where national data do not exist, approaches have to be made to all persons, which is both more costly and may reduce the proportion of people at high risk who participate.[7 10]

Although the models we have now seem to be fit for purpose, better models predicting a favourable risk:benefit ratio, and with the facility to modify this during incidence rounds are needed. Models need to be deployed in a way that facilitates participation among those eligible, particularly in the light of the evolving COVID-19 pandemic.

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