



Figure 1 Proposed study design to assess cost-effectiveness in the UK Lung Screen using spirometry and gene-based risk stratification to optimise lung cancer detection rate. LLP, Liverpool Lung Project model.²

UK Lung Screen (UKLS)) following the results of the National Lung Cancer Screening Trial. We agree that cost-effectiveness and defining who would most likely benefit from CT screening remain key issues to be resolved before CT screening can be offered routinely in clinical practice.²

First, cost-effectiveness is most likely to be achieved through optimising the risk assessment of those potentially eligible for CT screening¹ and maximising the number of cancers identified for each scan done. While historical data may assist in this risk assessment,² it is possible that biomarkers are required to better stratify this risk. In this regard, we and others have shown that a reduced forced expiratory volume in one second (FEV₁) is the single most important risk factor (and biomarker) for lung cancer susceptibility and is present in up to 80% of those diagnosed with lung cancer.³ We hypothesise that targeting those smokers with mildly or moderately reduced FEV₁ may help maximise picking up of 'treatable' lung cancer.³ Such an approach was reported in a small community-based study where lung cancer was detected in 6% of those who underwent baseline CT screening,⁴ much greater (by over threefold) than that reported by the National Lung Cancer Screening Trial and estimated in the UKLS (1–2%).² In the absence of abnormal lung function, other biomarkers such as gene-based risk stratification⁵ might have utility in identifying those at the greatest risk of lung cancer. We note that although neither lung function nor DNA sampling contributes to the Liverpool Lung Cancer Risk Prediction Model,² all UKLS participants will have these taken.²

Second, apart from optimising entry into a CT-based screening programme, cost-

effectiveness might also be improved by limiting subsequent CT screening according to the risk profile. In this regard, we hypothesise that smokers with normal lung function, no evidence of emphysema on baseline CT scan and/or 'low gene-based risk'⁵ might not require yearly scanning. Such a group might defer scanning (or increase the scanning interval), much like colonoscopy for bowel cancer screening is individualised according to the risk level.

Both these hypotheses could be examined in the UKLS where the 'single screen' design and DNA sampling enable a gene-based risk model to be examined with respect to predictability and survival (figure 1). We conclude that optimisation of patient selection and scan interval, through biomarker-based risk stratification, may help improve the cost-effectiveness of CT screening.

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CT screening for lung cancer: so near, yet so far

The UK Lung Screen team in their positional statement outlined the issues to be explored by the trial on CT screening for lung cancer.¹ Although it seems to be a large, well-planned study, we believe that there are some shortcomings in this study that may undermine its significance. There are several other aspects of CT screening that need to be investigated in order to determine the suitability of the screening and thus guide a national programme. The additional investigation areas may include:

1. Studying the number of unnecessary lung biopsies, invasive procedures and surgeries due to cancer screening and the morbidity and mortality caused by these procedures.
2. The risk of development of radiation-induced malignancy, both in patients undergoing routine yearly screening and in those subjected to serial CT scans for suspicious lesions. Some studies have shown significant risk of development of radiation-induced malignancies.²
3. Smoking abstinence behaviour in people undergoing screening. Concerns have been raised regarding smokers having a negative result on CT screening believing that they can continue smoking without any increased risk of dying from lung cancer.³ Such behaviour can expose them to other potentially fatal smoking-related diseases like chronic obstructive pulmonary disease and other malignancies.
4. Emotional and psychological effects of false positive results, which can significantly impair the life of the individual. Moreover, investigators are planning to include only those cases with >5% risk of

lung cancer according to the Liverpool Lung Project risk model, which will miss the opportunity to study the impact of screening in a low risk group population, and further the Liverpool Lung Project model may not take into account the separate risk factors working in different ethnic populations⁴ thus making its prediction less reliable in the cosmopolitan UK population where according to the 2001 census >15% of the population is non-white British.⁵

We hope that the investigators are open to our suggestions and will accept our ideas if they find some relevance in them.

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Authors' response

We thank Dr Tournoy for his interest in our article on the utility of endobronchial ultrasound-guided transbronchial needle aspira-

tion (EBUS-TBNA) for the diagnosis of tuberculous intrathoracic lymphadenopathy.¹

With regard to the patient selection in our study, we have acknowledged in the Discussion that the characteristics of patients with intrathoracic lymph node tuberculosis not submitted for EBUS-TBNA are unknown. This selection bias is an inherent problem in retrospective cohort studies, as only those patients suitable for EBUS-TBNA are included. Dr Tournoy would like to know the sensitivity of EBUS-TBNA for all cases in which tuberculous lymphadenitis is suspected; however, this is not reliably obtainable from a retrospective study. We have recently completed the recruitment to a prospective trial of EBUS-TBNA in patients with isolated mediastinal lymphadenopathy, which aims to answer this question (ClinicalTrials.gov identifier: NCT00932854).

We do not agree with Dr Tournoy's assertion that restricting the sample to patients with the condition overestimates the sensitivity. Indeed, the definition of sensitivity of a test is the number of patients diagnosed by the test (true positives) divided by the total number of patients with the condition (true positives + false negatives). Therefore, including patients without tuberculous lymphadenitis would not affect the analysis.

Dr Tournoy states that epithelioid granulomas without caseation are more likely to be consistent with sarcoidosis. However, this is based on a cohort of patients with suspected sarcoidosis and a low prevalence of tuberculosis.² In addition, he does not acknowledge the data from our article which show that this pathological criterion was associated with a positive culture of *Mycobacterium tuberculosis* in 34% of cases. The finding from our study that non-caseating granulomas obtained from EBUS-TBNA are consistent with tuberculosis in a setting of moderate to high disease prevalence is an important one. We are puzzled by the remark that lymph node necrosis (seen in the absence of malignant cells) is primarily consistent with cancer without reference to the prevalence of tuberculosis and malignancy in the population. Five out of the eight patients with lymph node necrosis in our study were culture positive for *M tuberculosis*. EBUS-TBNA is in clinical use in populations with high tuberculosis preva-

lence (eg, India), where the dogma presented by Dr Tournoy may not apply.

Finally, we do not agree that a limit should be set on the sensitivity of EBUS-TBNA for the diagnosis of tuberculous lymphadenitis. The emergence of rapid molecular techniques³ has the potential to improve microbiological yield further from EBUS-TBNA samples and this is also currently under investigation. We believe that EBUS-TBNA can provide clinicians with strong pathological evidence and microbiological proof of intrathoracic lymph node tuberculosis. Clinicians will already be aware that if microbiological results are negative, the predictive values of EBUS-TBNA pathology grades (none of which are entirely specific for tuberculosis) will depend on the context of the clinical features and the prevalence of tuberculosis in the population to which the patient belongs.

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