### RESEARCH LETTER

## Tuberculosis through the rose tinted spectacles of the EBUS endoscopist: be aware of the bias

I read with interest the article on the utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in tuberculous intrathoracic lymphadenopathy by Navani et al.[1]

EBUS-TBNA has been validated for the assessment of mediastinal nodes in lung cancer[2] and to obtain a diagnosis in (presumed) centrally located lung cancer[3] or sarcoidosis.[4] In addition to a recent report,[5] the study by Navani et al adds to the evidence for the use of EBUS-TBNA in cases of presumed tuberculous lymphadenitis. A sensitivity of 94% is reported, which might be too optimistic.

First, patients were selected in a peculiar way. The authors reviewed the files of all EBUS endoscopies and retrospectively selected those cases in which tuberculosis was finally found. Unfortunately, there is no information on how the patients were selected *beforehand*. The reported figure gives an indication of the sensitivity of EBUS in this particular setting; however, it does not give an answer to the more relevant question about the sensitivity of EBUS-TBNA for *all cases* in whom tuberculous lymphadenitis is suspected. There were potentially many patients with tuberculous intrathoracic lymphadenitis who were not sent for EBUS.

Second, the use of assessment tools (ie, EBUS) only in patients having the condition leads to an overestimation of sensitivity. Since there is no remedy for the over-estimation *in this series*, the results should be interpreted with caution.

Finally, three of the five pathology grades are grouped as compatible with tuberculosis. Two of these, epithelioid granulomas without caseation and necrosis are primarily compatible with sarcoidosis and cancer rather than tuberculosis,[4] despite suggestive symptomatology or an (undefined) response to medication. A more conservative analysis combining strict pathological and microbiological criteria would be informative.

Therefore, it might be appropriate to say that for tuberculous lymphadenitis, the sensitivity of EBUS is at the most 94%. Although I recognise the importance of EBUS, my reflections should serve as a reminder to doctors to exercise caution when their diagnosis of tuberculosis is based on the idea that the sensitivity of EBUS is 94% and that a negative EBUS excludes the disease.

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## CORRESPONDENCE

## Authors' response

We thank Dr Young for his comments on the recent UKLS position statement.[1] We are aware of the current studies on chronic obstructive pulmonary disease (COPD) and lung cancer. However, there is no validated lung cancer risk model in the UK which currently incorporates dynamic lung volumes that could be used in the UKLS trial. All the recruited individuals will have spirometry at the time that they are recruited into the UKLS trial, thus data will be available for developing the Liverpool Lung Project risk model.[2][3] We do not wish to focus on COPD risk groups for the pilot UKLS trial.

Smoking is the over-riding risk factor in lung cancer. Our measurements will provide further information concerning the potential for COPD as a useful factor in selecting populations that may benefit from screening. We do not have population-based spirometry in the UK to screen populations and there is an issue over the diagnostic crossover between COPD and asthma.

The search for molecular biomarkers and susceptibility genes, which may be used in early detection programmes, has proved challenging; although there are a number of promising candidates,[4—7] none, to date, has been validated to a level where they can be used in an early lung cancer clinical trial.

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## CT screening for lung cancer

We read with interest the recent opinion piece by Field *et al*[1] outlining plans for a CT screening trial in the United Kingdom (the
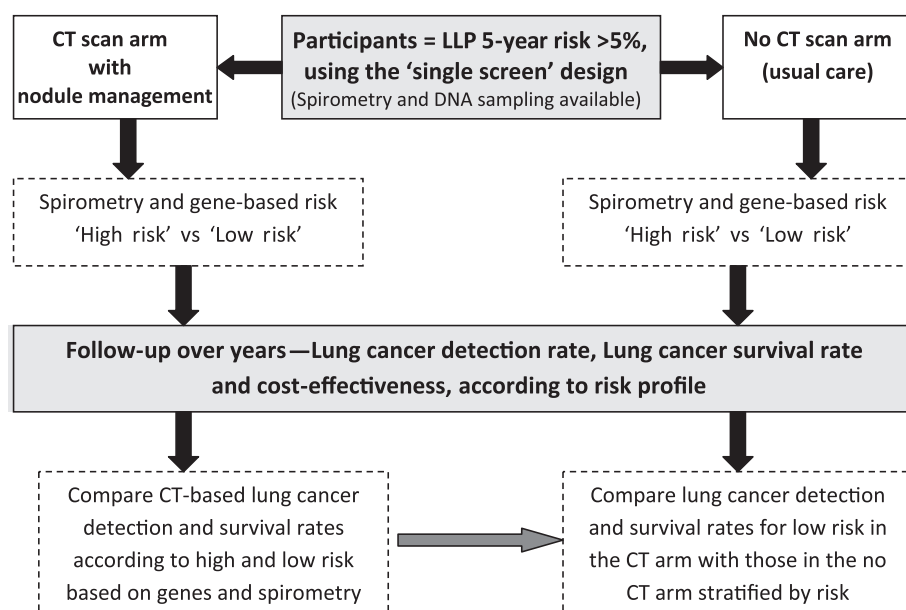
**Figure 1** Proposed study design to assess cost-effectiveness in the UK Lung Screen using spirometry and gene-based risk stratification to optimise lung cancer detection rate. LLP, Liverpool Lung Project model.[2]

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 screening[1] 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 ($FEV_1$) 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 $FEV_1$ 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 stratification[5] 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