UK Lung Cancer RCT Pilot Screening Trial

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UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening


ABSTRACT

Background Lung cancer screening using low-dose CT (LDCT) was shown to reduce lung cancer mortality by 20% in the National Lung Screening Trial.

Methods The pilot UK Lung Cancer Screening (UKLS) is a randomised controlled trial of LDCT screening for lung cancer versus usual care. A population-based questionnaire was used to identify high-risk individuals. CT screen-detected nodules were managed by a pre-specified protocol. Cost effectiveness was modelled with reference to the National Lung Cancer Screening Trial mortality reduction.

Results 247 354 individuals aged 50–75 years were approached; 30.7% expressed an interest, 8729 eligible and 4055 were randomised, 2028 approached; 30.7% expressed an interest, 8729

Conclusions The UKLS pilot trial demonstrated that it is possible to detect lung cancer at an early stage and deliver potentially curative treatment in over 80% of cases: health economic analysis suggests that the intervention would be cost effective, but this needs to be confirmed using data on observed lung cancer mortality reduction.

INTRODUCTION

Almost three-quarters of people with lung cancer present with advanced stage disease, when treatment has little effect on survival. In 2010 the US-based National Lung Cancer Screening Trial (NLST) was stopped 1 year early because a 20% relative reduction in lung cancer mortality had been achieved by low-dose CT compared with chest x-ray after three annual screens and 6 years of follow-up. Subsequent publications have identified a number of areas where improvements can be made. Six recommendations were made in the International Association for the Study of Lung Cancer (IASLC) CT screening workshop report, with a focus on future implementation. These were:

1. Optimisation of identification of high-risk individuals.
2. Development of radiological guidelines.
Lung cancer

5. Definition of criteria for surgical and therapeutic interventions of suspicious nodules identified through lung cancer CT screening programmes.

6. Development of recommendations for the integration of smoking cessation practices into future national lung cancer CT screening programmes.

Resolution of these issues is important to ensure that future national lung cancer screening programmes target a population at high enough risk of developing lung cancer while minimising the potential for harm, in a cost-effective way.5

The aims of the UK Lung Cancer Screening (UKLS) pilot trial were to demonstrate the effectiveness of risk prediction modelling for the selection of high-risk participants; to evaluate the use of volumetric analysis in the management of CT-detected nodules linked with pragmatic follow-up strategies; and to determine cost effectiveness based on modelling of the pilot UKLS approach.

METHODS
The UKLS trial received approval from the National Information Governance Board. Ethical approval for the study was given by Liverpool Central Research Ethics Committee in December 2010 (reference number 10/H1005/74). The trial was registered with the International Standard Randomised Controlled Trial Register under the reference 78513845.

The UKLS is a randomised controlled trial of low-dose CT (LDCT) screening versus standard care for the early detection of lung cancer in high-risk individuals. The study follows the Wåld Single Screen Design, as described previously.5

Sample size
We designed the pilot to give a precise estimate of the proportion of subjects complying with screening. A study size of 4000 and therefore 2000 in the intervention arm would enable us to estimate 80% compliance with a 95% CI not exceeding ±2%.

UKLS trial design
The Wåld single-screen design was adopted because it is the most economical approach in terms of the number of CT screening examinations needed for a fully powered trial (as it was originally planned that 32 000 individuals were to be randomised in the main UKLS trial). It will also provide early data on rates of cancers in the years following a screen, to inform the most appropriate ‘interval’ for subsequent screens. It will produce mortality results in a similar timeframe to the other major international multicentre screening trials, and allow us to synchronise our data. In addition, the single screen design does not have the problem of long-term compliance.

Identification of Individuals with a high risk of developing lung cancer
The eligibility criteria in the current two largest randomised controlled trials (NLST and NELSON) were based on smoking history and age,1–6. However, risk of lung cancer is also influenced by other factors that can be used to refine risk prediction and improve selection.

The Liverpool Lung Project (LLP) risk model was based on a case–control study.17 It is a multivariable conditional logistic regression model based on factors significantly associated with lung cancer (smoking duration, prior diagnosis of pneumonia, occupational exposure to asbestos, prior diagnosis of malignant tumour and early onset (<60 years) family history of lung cancer).7 The multivariable model was combined with age-standardised incidence data to estimate the absolute risk of developing lung cancer. The discrimination of the LLP was evaluated and demonstrated its predicted benefit for stratifying patients for CT screening by using data from three independent studies from Europe and North America.8

The LLP risk model includes all respiratory disease (COPD, emphysema, bronchitis, pneumonia and TB9) and all smokers (cigarettes, pipe and cigars) to select subjects with ≥5% risk of developing lung cancer in the following 5 years.10 The risk prediction model is available on http://www.mylungrisk.org.

Inclusion and exclusion criteria

Inclusion criteria
A 5-year lung cancer risk of ≥5%, based on the LLP risk prediction model,7 8 10 men and women aged between 50 and 75 years old, ability to provide fully informed written consent.

Exclusion criteria
Inability to give consent, comorbidity which would unequivocally contraindicate either screening or treatment if lung cancer were detected, thoracic CT performed within 1 year preceding the invitation to be screened, inability to lie flat.

Recruitment
We identified 249 988 individuals from population Primary Care Trust records, aged 50–75 years, residing in specific health-care areas (Liverpool, Knowsley, Sefton; Cambridgeshire, Peterborough, and Bedfordshire). Questionnaires were sent to 247 354 individuals to identify those at high risk (≥5% over 5 years) of developing lung cancer. The first UKLS approach questionnaire is available on the UKLS website (http://www.ukls.org) and was distributed by Radar, the third party data management company (http://www.marketingradar.com). A second questionnaire was sent to individuals considered to be at high risk, inviting them to participate in the UKLS trial (http://www.ukls.org). Recruited subjects were randomly allocated by simple computer pseudo-random number generation to either the intervention (LDCT) or control arms in a 1:1 ratio. Figure 1 illustrates the trial recruitment process.

CT
CT scans were performed on Siemens 128-slice scanners (Siemens, Erlangen, Germany) at Papworth Hospital, Cambridgeshire and Liverpool Heart and Chest Hospital (LHCH). In the initial phase of the trial, from November 2011 to December 2011, a Philips Brilliance 64 slice scanner (Philips, Best, The Netherlands) was used at LHCH, using the same acquisition parameters.

Thoracic CT images were obtained from lung apices to bases, during suspended inspiration, in a single breath hold and without the administration of intravenous contrast. Images were reconstructed at 1 mm thickness at 0.7 mm increments, using a moderate spatial frequency kernel reconstruction algorithm. Acquisition parameters (kVp and mAs) varied according to body habitus to achieve a CT dose index below 4 milliGray.

Reading methods
To optimise nodule detection, all baseline CTs were read by two experienced thoracic radiologists, one at the local trial centres (LHCH or Papworth Hospital) and one at a central site (Royal Brompton Hospital (RBBH)). All discrepancies were reviewed by a third thoracic radiologist at RBBH, who was the final arbiter. Once consensus had been reached, a letter was sent to the participant and their GP giving the results of the CT.

Readers were required to identify and record all lung nodules greater than 15 mm3 or 3 mm in maximum diameter (when
volumetry was not possible) as per the UKLS nodule management protocol (figure 2). CTs were read using nodule volumetry software (Siemens Syngo LungCare). Maximum intensity projections (MIPs) were used to aid detection.

**Nodule management**

Classification of CT findings was based on the UKLS radiology protocol, utilising nodule diameter and volume, on the Siemens LungCARE software platform. Nodule management is shown in figure 2; a summary is given below:

- No nodules or category 1 (benign) nodules: no further action required.
- Category 2 (small, probably benign) nodules: follow-up CT scan at 12 months.
- Category 3 (larger, potentially malignant) nodules: follow-up CT scan at 3 months and 12 months.

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**Figure 1** UK Lung Cancer Screening (UKLS) trial recruitment and implementation process. LDCT, low-dose CT scan; MDT, multidisciplinary team.
Category 4 (higher chance of malignancy) nodules: immediate referral to multidisciplinary team (MDT).

Nodules greater than 500 mm$^3$ or 10 mm maximum diameter at baseline (category 4) or nodules that demonstrated growth on follow-up CT (as defined by a volume doubling time <400 days) were referred to the local MDT for further assessment.

The nodule management protocol has many similarities to that used by the NELSON trial, except that a cutoff volume of 15 mm$^3$ was specified to minimise the risk of missing small lung cancers within the single screen design.

**Assessment of harms**

All procedures performed by the local MDTs were recorded along with any complications. Detailed psychological assessments were made at intervals during the study; these are the subject of separate planned publications.

**The proposed outcomes of the pilot UKLS Trial**

- Population-based recruitment based on risk stratification.
- Trial management through a web-based database.
- Define optimal characteristics of CT readers (radiologists vs radiographers).
- Characterisation of CT-detected nodules utilising volumetric analysis.
- Prevalence of lung cancer at baseline.

- Socio-demographic factors affecting participation.
- Psychosocial measures (cancer distress, anxiety, depression, decision satisfaction).
- Cost-effectiveness modelling.

Statistical treatment of data for this paper was restricted to description of numbers and percentages responding who were eligible, recruited and screened, with outcomes of the screening.

**Cost-effectiveness modelling based on UKLS pilot data**

A full UKLS trial was planned to follow the pilot: this would have randomised an additional 28 000 subjects but was not funded. The pilot UKLS trial was not powered to evaluate mortality reduction and this short follow-up period precluded adopting the conventional approach to trial evaluation, namely, the measurement of long-term costs and outcomes in the test and control arms, and the comparison thereof. Thus, the observational element of the economic evaluation was restricted to those events and findings that occurred within the active trial period. The detailed modelling methodology for calculating the UKLS cost effectiveness is described in the online supplementary section.

**RESULTS**

**Recruitment**

From the 247 354 people sent questionnaires, 148 608 (60.1%) were non-responders (no questionnaire returned), 22 788 (9.2%) were negative responders (non-participation...
questionnaire returned) and 75,958 (30.7%) were positive responders (questionnaire returned; willing to participate). Of the positive responders, 8,729 (11.5%) were classified by the LLPv2 as high risk, with a risk of ≥5% of developing lung cancer over the next 5 years (mean LLPv2 risk score=8.8% versus 1.0% for the low risk group). A total of 59,678/729 (68.4%) high-risk responders returned the second questionnaire and agreed to participate; 1,291 of these were subsequently excluded for the following reasons: they did not meet the inclusion criteria; they had not completed the eligibility questionnaire correctly; they replied after maximum trial recruitment numbers had been reached; or they were unable to give fully informed consent. Five hundred and eighty-two individuals either changed their mind or failed to attend clinic, and a further 33 attended the recruitment clinic but declined to consent. No stratification criteria were used. In total, 4061 individuals (5.3% of all positive responders, and 46.5% of all high-risk positive responders) consented and were recruited into the UKLS.

Figure 3 shows the participant flow from invitation through to randomisation. Figure 4 provides the percentage of UKLS positive responders (n=75,958) with an LLP risk of ≥5%, by individual age; there was a steady increase with age in the percentage of people at high risk, with very low numbers at age 50–54.

A total of 73,934 (97.3%) of the positive responders gave information about their smoking habits: 43.4% were never smokers, 14.7% current smokers and 39.3% ex-smokers. A total of 22,024 (96.6%) of the 22,788 negative responders gave information on smoking habit: 51.3% were never smokers, 9.1% current smokers and 36.2% ex-smokers.

**CT screened participants**

A total of 1,994 participants underwent CT by July 2014; 42 participants (2.1%) were diagnosed with lung cancer, 34 (1.7%) at baseline and 8 (0.4%) were diagnosed within 12 months with follow-up CT. Characteristics of individuals in both arms of the trial were very similar (table 1). The date of censoring was 30 September 2014.

**NODULES AND MANAGEMENT**

There were 1,015 (50.9%) subjects with category 2–4 nodules; 479/1994 (24%) subjects with category 2 nodules underwent a 12-month repeat scan. Seven of 479 (1.5%) were referred to the MDT, of whom 1/479 (0.2%) was diagnosed with lung cancer (table 2).

Four hundred and seventy-two subjects (23.7%) had category 3 nodules and underwent a 3-month interval CT. Forty-three of the participants (9.1%) were referred to the MDT. A total of nine (1.9%) lung cancers were diagnosed; two at month three and seven at the 12-month repeat scan.

Of 64 participants with category 4 nodules who were referred directly to the MDT, 32 (50%) had lung cancer (table 3).

**Diagnostic workup and false positives**

In the UKLS, we defined false positives as those requiring further diagnostic investigation more immediately than a repeat annual screen, but who subsequently did not have lung cancer.
This is because future screening programmes are likely to include annual or biennial screens. Overall, 951/1994 (47.7%) of subjects underwent at least one further CT after the initial screen.

For complete clarity, the proportion of false positive tests is now provided in two ways, which allows an appreciation, in a patient-centred approach, of the variable impact on the subject in a trial or the patient in a programme. A 'false positive' that mandates referral to the lung cancer MDT will usually be associated with significant psychological distress and additional more or less invasive investigations with, in some cases, definitive treatment. An individual with a false positive test so defined is thus more likely to suffer harm than one defined in a different way; that is, those subjects who are recalled solely for further CT imaging to clarify the nature of a nodule. The latter is best termed 'interval imaging rate' and may, in screening programmes, merely mean continuing in the programme rather than referral to the MDT. For this reason, all category 3 lesions without cancer are reported separately as false positives warranting interval imaging. Category 2 findings are not classified as false positives warranting recall as the cancer rate was found to be so low in this study that interval imaging would not be recommended.

Thus on examining the number of UKLS participants referred to the MDT clinic, the false-positive rate is 3.6% (114/42/1994 = 3.6); whilst the interval imaging rate is 23.2% (472-9/1994).

In total, 114/1994 (5.7%) participants were referred to the MDT, of whom 42 (2.1% of all screened) had lung cancer.

**Pathology**

Of the 42 screen-detected cancers, there were 25 adenocarcinomas, 12 squamous cell carcinomas, 3 small cell carcinomas, 1 typical carcinoid, and 1 bronchogenic carcinoma. Twenty-eight of 42 (66.7%) lung cancers were detected at stage I and 8/42 (19%) at stage II (table 3). In total, 36/42 (85.7%) were stage I or II.

**Treatment**

Thirty-five of 42 subjects (83%) had surgery as their primary treatment, with eight having adjuvant chemotherapy. Thirty-three of the 36 patients with stage I and II lung cancer had surgery (91.6%) and a further two had radical radiotherapy (total 97%). In the seven patients who did not undergo resection, lung cancer diagnoses were made radiologically in one individual and via tissue biopsy in six patients. Four patients...
Table 2  Numbers of UKLS individuals in each Nodule category; MDT referral and the number of confirmed lung cancers.

<table>
<thead>
<tr>
<th>Nodule category (management)</th>
<th>Cat 1 (discharged)</th>
<th>Cat 2 (repeat scan at 12 months)</th>
<th>Cat 3 (repeat scan at 3 months then 12 months)</th>
<th>Cat 4 (immediate MDT referral)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number in category</td>
<td>979</td>
<td>479</td>
<td>472</td>
<td>64</td>
<td>1994</td>
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<tr>
<td>Number referred to MDT</td>
<td>0 (N/A)</td>
<td>7</td>
<td>43</td>
<td>64</td>
<td>114</td>
</tr>
<tr>
<td>Number of confirmed lung cancers</td>
<td>0 (N/A)</td>
<td>1</td>
<td>9</td>
<td>32</td>
<td>42</td>
</tr>
</tbody>
</table>

MDT, multidisciplinary team.

Table 3  Lung cancer diagnosed in pilot UK Lung Cancer Screening (UKLS)

<table>
<thead>
<tr>
<th>UKLS case No</th>
<th>Baseline nodule category*</th>
<th>Sex</th>
<th>Age</th>
<th>TNM</th>
<th>Final Stage</th>
<th>Diagnosis</th>
<th>Treatment</th>
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</thead>
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<tr>
<td>1</td>
<td>4</td>
<td>M</td>
<td>59</td>
<td>pT1a pN0</td>
<td>IA</td>
<td>Adenocarcinoma</td>
<td>Surgery</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>M</td>
<td>66</td>
<td>pT1a pN0</td>
<td>IA</td>
<td>Adenocarcinoma</td>
<td>Surgery</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>M</td>
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<tr>
<td>4</td>
<td>4</td>
<td>M</td>
<td>55</td>
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<tr>
<td>5</td>
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<td>IA</td>
<td>Adenocarcinoma</td>
<td>Surgery</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>F</td>
<td>64</td>
<td>pT1a pN0</td>
<td>IA</td>
<td>Adenocarcinoma</td>
<td>Surgery</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>M</td>
<td>67</td>
<td>pT1b pN0</td>
<td>IA</td>
<td>Small cell carcinoma</td>
<td>Surgery/chemotherapy</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>M</td>
<td>62</td>
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<td>Squamous cell carcinoma</td>
<td>Surgery</td>
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<tr>
<td>9</td>
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<td>Surgery</td>
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<td>Surgery</td>
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<td>69</td>
<td>cT1a cN0 cM0</td>
<td>IA</td>
<td>Adenocarcinoma</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>40</td>
<td>3 (12 months)</td>
<td>M</td>
<td>71</td>
<td>pT1a pN0</td>
<td>IA</td>
<td>Adenocarcinoma</td>
<td>Surgery</td>
</tr>
<tr>
<td>41</td>
<td>3 (12 months)</td>
<td>F</td>
<td>75</td>
<td>cT4 cN2 cM1b</td>
<td>IV</td>
<td>Adenocarcinoma</td>
<td>Surgery (non-pulmonary)</td>
</tr>
<tr>
<td>42</td>
<td>2</td>
<td>F</td>
<td>66</td>
<td>pT1a pN0</td>
<td>IA</td>
<td>Adenocarcinoma</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

with benign disease had surgery (benign resection rate of 10.3% (4/39)). Details of the UKLS patients with lung cancer with final pathology, TNM, stage and management are shown in Table 3.

**Cost effectiveness**

A detailed description of the results of the health economics modelling is given in the online supplementary section. The baseline estimate for the incremental cost-effectiveness ratio (ICER) of once-only CT screening relative to symptomatic presentation, under the UKLS protocol, was £8466 per quality adjusted life year (QALY) (£5542 to £12 569).

**DISCUSSION**

The UKLS pilot has demonstrated that, by using a population-based approach and a validated risk assessment model, it is possible to detect lung cancer at an early stage using LDCT screening. Over 85% of lung cancers detected were stage I or II, and over 90% of these cases were able to have potentially curative treatment.

Overall, there was a 1.7% prevalence of lung cancer at baseline which is higher than that reported by the NLST16 or NELSON11 12 trials. This reflects the relatively high minimum risk threshold using the LLPv2 risk model (≥5% over 5 years).

The postal questionnaire approach achieved a 30.7% positive response rate to the initial mailing, a good response rate for a consent approach for possible screening for small nodules (10.3%). The trial has also demonstrated that, by using a population-based protocol, was £8466 per quality adjusted life year (QALY) (£5542 to £12 569). The modelled ICER of once-only CT screening under the UKLS protocol was of the order of £9000 per QALY. This is broadly consistent with the ICERs of other recent studies, once allowance is made for differential efficiency of screening protocols. The ICER would be less favourable if there were substantial overdiagnosis but better if smoking cessation were allowed for differential efficiency of screening protocols. The ICER would be less favourable if there were substantial overdiagnosis but better if smoking cessation were improved. The prevalence of lung cancer was consistent with the risk status of the UKLS recruits, so substantial overdiagnosis is unlikely.

The comparison of the NLST and UKLS cost-effectiveness approaches is outlined in Table 4. The UKLS ICER is about one-fifth of the NLST’s costs ($81 000), mainly explained by the

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of cost-effectiveness approaches used in the National Lung Cancer Screening Trial (NLST) and UK Lung Cancer Screening (UKLS)</th>
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</thead>
<tbody>
<tr>
<td><strong>UKLS</strong></td>
<td><strong>NLST</strong>16</td>
</tr>
<tr>
<td>1 Yield=2.1% of persons screened</td>
<td>Yield=2.0% of persons screened</td>
</tr>
<tr>
<td>2 Single prevalence screen. Screening and workup costs per person=£212 to £327 at current exchange rates (7 July 2015)</td>
<td>3 screens to produce similar yield Screening and workup costs per person screened=£1965 (table 2)</td>
</tr>
<tr>
<td>3 Net treatment costs per person (screen-detected vs no screening)=£60 to £92</td>
<td>Net treatment costs per person (screen detected vs no screening)=£175</td>
</tr>
<tr>
<td>4 Costs of patient time and travel to appointments are NOT included in total costs: the evaluation adopts an NHS perspective, as recommended by NICE</td>
<td>Costs of patient time and travel to appointments are included in total cost: the evaluation adopts a social perspective, as recommended by the US Panel on Cost-Effectiveness in Health and Medicine</td>
</tr>
<tr>
<td>5 Outcome estimate calculations based on life table survival estimates</td>
<td>Outcome estimates calculations based on life table survival estimates</td>
</tr>
<tr>
<td>6 Incremental quality adjusted life years (QALYs) gained per person screened=0.03</td>
<td>Incremental QALYs gained per person screened=0.02 overall, but 0.03 in the age range 60–69</td>
</tr>
<tr>
<td>7 UKLS modelling based on 1 year £8466 per QALY gained (CI £5542 to £12 569)</td>
<td>NLST $81 000 per QALY gained (5% CI $52 000 to 186 000). Calculations based on quintiles 4 and 5, accounts for a significantly higher number of lung cancer deaths: costsings: 4th quintile $32 000/QALY; 5th quintile $52 000/QALY (ie, $20,921; $33,996)</td>
</tr>
</tbody>
</table>

NICE, National Institute for Health and Care Excellence.
differences in unit costs and in the intensity of resource use to detect and manage the same proportion of cancers. The UKLS was a single screen compared with the NLST’s three annual screens but both gave similar yields of lung cancer.

One of the limitations of our analysis is that the mortality benefit had to be estimated from NLST. Interestingly, estimates from both NLST and UKLS were similar, despite the fact that UKLS targeted a higher risk group (table 4). The main shortcoming of the UKLS is that it is a pilot study and is not powered for a long-term mortality comparison in isolation. However, it is planned to pool the UKLS data, including mortality data, from both arms with the European screening trials,\textsuperscript{5,7} including NELSON, in 2016.

In summary, the UKLS pilot has shown that CT screening in the UK is possible using a risk prediction model that avoids the selection of people at very low risk who are unlikely to benefit,\textsuperscript{13,18} and a nodule management algorithm that effectively manages indeterminate CT findings, yet detects a high number of early stage lung cancers.

Taking the UKLS pilot trial data in consort with the NLST mortality data, health economics modelling showed a promising ICER. However, if CT screening is adopted, efforts to maximise cost effectiveness should be made, such as integrated smoking cessation. The results from the NELSON trial and the pooled UKLS and NELSON trial data will likely influence the decision to undertake lung cancer screening in the UK.\textsuperscript{19,20}

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**REFERENCES**


Lung cancer


