Title:
CT Screening for lung cancer: is the evidence strong enough?

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CT Screening for lung cancer: is the evidence strong enough?

The prevailing questions at this time in both the public mind and the clinical establishment is, do we have sufficient evidence to implement lung cancer CT screening? If not, what is outstanding?

This review will address the twelve major areas where we need to assess whether we have sufficient evidence to proceed to a recommendation to implement CT screening in Europe. These twelve areas are illustrated in Figure1, with colour codes as to our current status in 2015, where green indicates we have sufficient evidence, amber is borderline evidence and red requires further evidence.

Background: Lung cancer is an important health problem

Lung cancer is an important cause of ill-health and is the second commonest cancer in men and women with around 44,488 new cases diagnosed in the UK each year. The number of deaths in 2012 was 35,371, making lung cancer the commonest cause of cancer death in the UK for both men and women (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer). In the European Union (EU-28) 268,000 deaths predicted in 2012 (http://globocan.iarc.fr/old/FactSheets/cancers/lung-new.asp). The main reasons why lung cancer outcomes are so poor are that around 70% of patients first present to specialist care with incurable advanced disease and current treatment at this stage has very little effect on mortality. More than one third of all lung cancer patients die within three months of diagnosis, despite having multiple visits to their GPs before their diagnosis[1]. However, if a patient's lung cancer is identified at an early stage, then the clinical outcome is greatly improved and this is a strong argument for seriously considering a national screening programme.

Figure 1 (Insert here)

Reduction in smoking over the last 50 years has made a massive impact on lung cancer mortality and smoking cessation interventions are very cost effective. Research

is now focused on increasing the effectiveness of smoking cessation and one recent approach has been to offer financial incentives. A recent randomised controlled trial of four financial-incentive programmes for smoking cessation found that that reward-based schemes did in fact lead to sustained abstinence, however it would appear that the public acceptability of such an approach discourages their adoption [2]. Smoking cessation is known to be greater when an individual experiences a significant health event, such as myocardial infarction. CT screening may also represent a significant health event and there is some evidence that cessation rates are increased above background rates in screening trials [3]. Thus building in smoking cessation, tailored to screenees is an important adjunct that is likely to increase cost effectiveness and potentially decrease all-cause mortality.

The financial burden of lung cancer is considerable: the estimated cost to the UK economy is £2.4 billion each year, £9,071 per patient annually. This is far higher than the cost of any other cancer despite survival rates being among the lowest. More curative treatment and prevention resulting from integrated screening and smoking cessation programmes has the potential to reduce these costs [4].

1. The evidence for a validated lung cancer screening test in Europe (Green).

The first major breakthrough for lung cancer screening came with the publication of the USA National Lung Cancer Screening Trial (NLST) [5], which was the first major RCT for lung cancer Low Dose Computed Tomography (LDCT) screening. NLST recruited over 53,000 people aged 55–74, with a 30 pack-year smoking history, who had smoked within 15 years. These subjects were randomised to LDCT or chest X-ray, with lung cancer mortality as the outcome. NLST reported a 20% relative reduction in lung cancer mortality in the LDCT arm[6]. Furthermore, all-cause mortality was reduced by 6.7% in the low-dose CT group compared with the X-ray group. This publication provided great optimism for the lung cancer screening community, as it provided the first evidence that LDCT screening saved lives.

The recommendations from the first IASLC SSAC workshop represented the only truly international view on screening and reported shortly after the publication of the NLST trial [7]. The recommendations were:

(i) Optimisation of identification of high-risk individuals;
(ii) Development of radiological guidelines;
(iii) Development of guidelines for the clinical work-up of indeterminate nodules;
(iv) Development of guidelines for pathology reporting;
(v) Definition of criteria for surgical and therapeutic interventions of suspicious nodules identified through lung cancer CT screening programmes;
(vi) Development of recommendations for the integration of smoking cessation practices into future national lung cancer CT screening programmes.

It is of note that many of the above areas of concern have been investigated in depth following the NLST publication, which included ensuring that future lung cancer screening programmes would target the high risk populations who had the greatest risk of developing lung cancer, whist minimising the potential for harm, in a cost effective manner [8]. During the intervening years after the NLST publication, five clinical and professional groups in the USA have also provided in-depth recommendations, which are naturally focused on the USA clinical practice. All of these professional groups supported the implementation of CT screening, with varying details on the definition of risk groups and the screening methodology. However, in 2014, the US Preventive Services Task Force (USPSTF) recommended implementation of LDCT screening. The USPSTF commissioned an independent analysis of the evidence, which proposed that lung cancer screening should be offered to individuals of comparable risk to NLST, but with an extension of the upper the age limit to 80 years [9]. The USPSTF recommended that screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. Recently, Medicare, has agreed to cover the costs of screening but they did stipulate a number of stringent requirements for inclusion.

2 Participation –Recruitment of the hard to reach (Red)

Added to the issues identified by the international workshop above is that of participation in CT screening. The participation rate in breast cancer screening programmes is around 70% and for colorectal around 60%. Lung cancer incidence is progressively greater with lower socioeconomic status. The lower socioeconomic

groups are often hard to engage in healthcare interventions and therefore it is important that ways to maximize participation rates are explored. One programme, underway in the UK is the Accelerate, Coordinate and Evaluate initiative, funded by Cancer Research UK and Macmillan. This is looking at novel ways to recruit people, for example by using mobile CT scanners.
(http://www.cancerresearchuk.org/health-professional/early-diagnosis-activities/ace-programme/ace-programme-projects#ACE_projects1)

NLST provides compelling evidence that CT screening should start as soon as possible but there are concerns about how it should be implemented and whether it will be cost effective. There are a number of European trials, the largest of which is the Dutch-Belgian NELSON trial, which is due to report on mortality within the next year. Thus, when pooled with results from other European trials including the pilot UK Lung cancer screening trial (UKLS) will be able to answer most of the remaining questions. Already these trials have provided important information about optimal radiology, nodule management, screen interval and estimated cost-effectiveness. Thus, European health care services may be in a position to make a final decision on implementing lung cancer screening within the next few years.

It is now internationally acknowledged that if lung cancer screening is not implemented in centres of excellence, it is highly unlikely that we will still see the same mortality advantage and there is a possibility that there will be a higher morbidity associated with CT screening programmes.

2. Evidence to Target high risk populations – using risk prediction modelling (Green)

One of the major drivers in ensuring that the benefits of implementing lung cancer screening outweigh the harms from screening, is to target individuals with a high risk of developing the disease. The future implementation of lung cancer screening requires the accurate identification of the individuals who will benefit the greatest from LDCT screening programmes, thereby ensuring the benefits outweigh the harms from screening. The current recommendations from the USPSTF, which are mainly based on the NLST trial, include screening all individuals between the ages of 55 and

80 with a smoking history of 30 pack-years or more [10]. In-depth analysis of the NLST has shown that there were significant differences in the number of lung cancer cases detected based on their underlying risk, regardless of whether the participants fitted the NLST entry criteria: 60% of participants at highest risk for lung-cancer death accounted for 88% of the prevented deaths, whereas the 20% of participants at lowest risk accounted for only 1% of prevented lung-cancer deaths) [11]. Put another way,5276 individuals in the lowest risk quintile had to be screened to prevent one cancer death and this resulted in the greatest number of false positives. This compares with the highest risk quintile where 161 individuals needed to be screened to prevent a lung cancer death. These data argue for a reassessment of the lung cancer risk criteria.

The PLCO $_{M2012}$ risk model, was used to evaluate the risk threshold for selecting individuals for screening and compared the efficiency with the USPSTF criteria [12]. The mortality rates among NLST participants screened with CT were found to be consistently lower than the mortality rates in the chest X-ray arm. Furthermore, the $PLCO_{M2012}$ improved the sensitivity and specificity of the selection of individuals for lung cancer screening over the UPSTF criteria. The major limitation of utilising the $PLCO_{M2012}$ risk $\geq$0.015 threshold for selecting individuals for LDCT screening trials, is that the evaluation was not based on a cost-effectiveness model. To date, the only lung cancer risk prediction model, which has been utilised in the recruitment of participants into a CT Lung Cancer Screening RCT, is the Liverpool Lung Project (LLP_{v2}) risk model in the UKLS [13]. The LLP_{v1} risk model was based on a case-control study [14] utilising conditional logistic regression to develop a model, based on risk 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) and family history of lung cancer) [14]. The multivariable model was combined with age-standardised incident data to estimate the absolute risk of developing lung cancer. The LLP risk model was evaluated in three independent studies from Europe and North America (22) and demonstrated its predicted benefit. The LLP_{v2} model included all respiratory disease and all smokers (cigarette, pipe and cigar) and was used to select high-risk individual in the UKLS [15]. UKLS randomised subjects were selected on the basis of their $\geq$5% risk of developing lung cancer in the next five years. Overall, there was a 1·7%

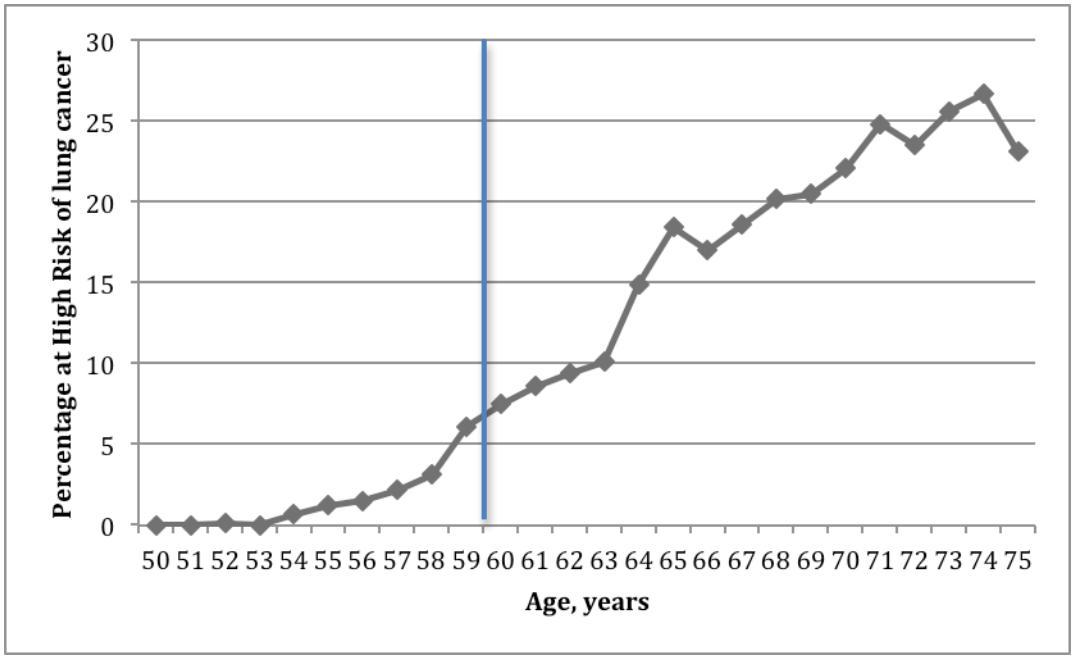
prevalence of lung cancer at baseline [16] which is higher than that reported by the NLST[17] or NELSON [18, 19] trials.

4. Screen a specific age range 60-75 years (Green)

An in-depth analysis of the UKLS trial data with respect to the LLP_{v2} risk status, clearly indicates that there is a significant increase in the population approached at the age of 58.

In the UKLS trial, the positive response rate ranged from 26.6% in the 50-55 age group to 35.0% in the 61-65 age group and then dropping to 27.6% in the 71-75 age group. Age is a major component of all lung cancer risk models including the LLP_{v2} risk model, where only 82 out of 16,273 positive responders (i.e. 0.5%) in the 50-55 age group were classified as high risk, compared to 2,046 (24.8%) in the 71-75 group. The 50-55 age group had the lowest positive response rate and were the least likely age group considered of being at high risk of lung cancer. In the UKLS, in the 50-55 age group, only 29 of 61,168 individuals originally approached (0.05%) were recruited to the RCT. In UKLS, approximately 95% of people at high risk were 60 or greater. thus this age should be chosen to start to initiate a screening programme.

Figure 2 Percentage of UKLS positive responders (n=75,958) with an LLP risk of $\geq$5% over 5 years, by individual year of age.



5. LDCT is a highly sensitive test for lung cancer (Green)

Modern CT scanners have been shown to have a sensitivity for detecting cancer of over 95% but also are able to reduced the effective radiation dose to below 1.6mSv, which is roughly the amount of annual background radiation, compared to 8mSv from a regular CT of the thorax [8, 20]

6. Identify 'indeterminate' nodules (Green)

There is now a large body of literature providing guidance on the detection, characterisation and management of indeterminate lung nodules which are frequently benign. Management protocols based on interval imaging with volumetric measurement have been shown to be effective in correctly identifying malignant lesions and minimizing the need for invasive tests. [18] [17]. The preferred method in the US is to rely on diameter measurements using manual electronic calipers. However this is known to be less accurate and less reproducible that volumetric measurements. In Europe the NELSON, UKLS, DLCST, LUSI and MILD studies have all used volumetric analysis [21]. Volumetry can more reliably detect growth,

defined as a 25% change in volume between the first and the second scan [18] than manual diameter measurement, defined in NLST as a 10% increase in diameter [17].

The nodule growth definition and care pathway used within in the UKLS trial is shown in Figure 1, which had many similarities to the NELSON methodology. In the NELSON trial, nodules less than 50 mm^3, were classified as negative, greater than 500mm^3 as positive; 50 to 500mm^3 as indeterminate [18]. Indeterminate nodules underwent a 3-month follow-up LDCT to assess for growth. Volume doubling times (VDTs) [22] were then used to distinguish between positive screens (VDT<400 days) requiring additional diagnostic procedures, and negative screens

The recent publication from the NELSON trial team has provided further insight into the judgement calls based on nodule volume measurements and volume doubling time [23]. Recently the British Thoracic Society produced the 'Magna Carta' of nodule decision guidelines [24], which has a major overlap with the current practices in CT screening programmes that advocate utilising CT nodule volumetric based measurements in conjunction with volume doubling times.

A risk prediction based approach has been developed to assess indeterminate nodules through risk assessment modelling and attempting to ascertain which nodules are at the highest risk of being malignant and thus require immediate intervention apart from utilising radiological imaging. This was undertaken using two Canadian cohorts, which included participants in the Pan-Canadian Early Detection of Lung Cancer Study and participants involved in chemoprevention trials at the British Columbia Cancer Agency (BCCA). The final outcomes of all nodules of any size that were detected on baseline low-dose CT scans were tracked. The rates of cancer in the two data sets were 5.5% and 3.7%, respectively. It is of note the predictors of cancer in the model included older age, female sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in the upper lobe, part-solid nodule type, lower nodule count, and also spiculation. The ROC was found to be 0.90 [25].

The NELSON investigators have undertaken an in depth analysis of lung cancer probability, based on nodule diameter, volume and volume doubling time, utilising their data on 7,155 individuals. Lung cancer had a low probability in participants with

a nodule volume of <100mm^3 or < 5mm diameter (0.6%); which was not significantly different from individuals with no nodules. Lung cancer in indeterminate nodules 100-300mm^3 or diameter 5-10mm was 2.4%. However, when volume doubling time (VDT) was also taken into account, those with a VDT of 600 days or more has a risk of 0.8% , VDT of 400-600 days was 4.0% and a VDT of 400 days or less was 9.6% [26]. These data provided further evidence that nodules with a diameter of less than 5mm or a volume less than 100mm^3 was not predictive of cancer and maybe considered the most appropriate methodology for any future lung cancer screening programme.

Reporting of false positives has varied in the literature. In NLST, any finding of a nodule ≥4mm diameter was classed as a false positive whereas NELSON defined categories of nodules that merely required follow-up LDCT as intermediate. In the UKLS trial, this distinction has been further clarified according to the variable potential impact on the subject in a trial or the patient in a programme. A finding that turns out not to be cancer yet 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 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 investigate the nature of a nodule. The latter situation has been termed "Interval Imaging Rate" and may, in screening programmes, merely mean continuing in the programme rather than referral to the MDT. Thus the definition of 'False Positive' and 'Interval Imaging Rates' in the UKLS trial, encapsulates the concept of the level of harms to the trial participants. The UKLS false positive rate was 3.6% and the interval imaging rate was 23.2%, very similar to the false positive and intermediate finding rates in NELSON of 19% and 3.6% . In NLST, the false positive rate (at least 4mm diameter nodule) was 24.2% of all CTs [17]. This difference is entirely due to the different definitions. [27] [18]. While the rate of interval imaging investigation might be acceptable, there is clearly room for better classification of the risk posed by nodules and for reduction of this rate.

7. Referral to MDT in Centre of Excellence (Green)

The NLST, NELSON and the UKLS all referred trial participants to the MDT for clinical workup. There is no internationally agreed protocol for the work-up of CT detected nodules that meet criteria for referral for further investigation. Several guidelines are available for the management of lung cancer which apply to pulmonary nodules with a high chance of malignancy. The first step for a growing or larger nodule (>10mm or 500mm^3 in NELSON and UKLS) is to do a PET-CT. In the recently published BTS guidelines on the investigation and management of pulmonary nodules, it is recommended that this is followed by a further risk assessment using the Herder model [24, 28]. Management is then guided by a combination of the risk of malignancy, fitness of the patient and most importantly, patient preference. For low risk (<10%) further imaging follow-up is preferred, for intermediate risk (10-70%) biopsy to confirm the diagnosis is preferred and for high risk >70% resection or treatment may be offered as a first choice after a fully informed discussion. Other guidelines give a similar message although risk categories vary and there is no use of the Herder model (AUC >0.9 in validation studies) . Along with nodule management it is important to accurately assess fitness for treatment and treat comorbidities [29, 30].

8. Treatment of Lung Cancer (Green)

Screen-detected lung cancer is mostly early stage and therefore amenable to curative treatment. The accepted gold standard is surgical resection. Current guidelines recommend lobectomy as the preferred operation, although sub-lobar resection may be performed if lung tissue needs to be spared owing to poor baseline lug function. Lobectomy has been shown to be superior to sub-lobar resection although the latter included both wedge resection and anatomical segmentectomy [31, 32] and the groups were dissimilar. There is currently some debate about whether anatomical segmentectomy is as good as lobectomy, especially for sub 2cm lesions [33, 34] . Localization of smaller pulmonary nodules can be achieved by a variety of preoperative techniques including radiologically guided injection of markers or placing of hook wires. No one technique has been shown to be superior so that the technique used will be dependent on local expertise and resources[24]. If surgery is

not possible due to patient fitness then radical radiotherapy is indicated, and because lesions are often small, stereotactic ablative radiotherapy (SABR) is preferred. The latter has been shown, in one propensity matched study, to be equivalent to surgery [35]. Three RCTs of surgery vs. SABR have failed to recruit but a further one is currently underway in the UK (SABRTOOTH).

9. Mortality Data on LDCT Screening (Amber in Europe)

There is only one trial to date with provides level one evidence for mortality data in lung cancer screening trials. The NLST showed a 20% gain in mortality in the CT arm compared to the chest X-ray arm of the trial. However, the trial design chosen by the NLST does beg the question would this figure have been different if the trial had had a no-screen arm and thus potentially a higher mortality result might have been found. Three European trials, which were not adequately powered have reported on their mortality data, none of which should any significant increase in mortality in the CT screened arm [36-38] and thus can not be considered as level one evidence. This leaves Europe awaiting the outcome of the NELSON trial, to provide evidence on e way or the other on whether CT screening in Europe will have a significant mortality impact.

Only the NELSON trial is powered at 80% to show a lung cancer mortality reduction of at least 25% 10 years after randomisation [39-41]. Three other European trials have published early mortality data. In two of the trials, the intervention group was offered annual low-dose CT screening [36, 42]. In the third, there were two active intervention groups, annual and biennial CT screening [43]. These three European trials, being underpowered and with suboptimal follow up periods, showed no significant reduction in lung cancer mortality. However, a meta-analysis including NLST yielded an overall mortality reduction of 19% (RR = 0.81, 95% CI 0.70-0.92), very similar to the result of the NLST alone [8] .

Analysis of mortality data from NELSON may be possible in 2016 and there is the intention to pool results of the UKLS trial [44]. The NLST is the dominant driver for implementation of LDCT screening in the USA but has not been accepted as the final decision in Europe; thus the reason why this section is scored “red”.

10. Cost effectiveness of LDCT screening (Amber in Europe)

In order to demonstrate that cancer screening would be cost effective by means of a randomised controlled trial requires the estimation of: the net costs of screening over detection via symptomatic presentation amongst trial subjects; net benefits, in terms of additional life expectancy on the part of screened subjects; the ratio of net benefits to net costs incurred. However, this ratio of benefits to costs must be consistent with society's attitude to the acceptable value for money in securing health gains. In the UK, the current convention for acceptability in the public health care system is £20-30,000 per quality-adjusted life year (QALY) gained[45].

The NLST has published an estimate of $81,000 per QALY as its mean ICER[46]. This figure is about four times greater than the currently acceptable figure within the UK. However, as the authors have provided a great deal of data on how these figures were calculated, it has become clear that if the NLST had focused on the 40% of participants at highest risk, then the intervention becomes more cost effective, with the ICER halved. [46].

Pyenson and colleagues [47] have modeled the cost and cost-effectiveness of LDCT lung cancer screening of the Medicare population at high risk of lung cancer in the USA. Utilising the current Medicare costs from the 2012 Centers for Medicare & Medicaid Services (CMS) beneficiary files and these were forecasted to 2014, based on specific US projections. They estimated that ~ 4.9 million high-risk Medicare beneficiaries would meet the USPSTF criteria for lung cancer screening in 2014 in individuals aged 55 to 80 years of age, with an estimated cost of $241 per person screened. The conclusion was that screening would be highly cost-effective, at <$19,000 per life-year saved for the Medicare beneficiaries and that an additional 358,134 individuals with lung cancer (current and ex-smokers) would be alive in 2014. It is of note that without screening, the Medicare patients with newly diagnosed lung cancer have an average life expectancy of approximately 3 years, much greater than the average seen globally.

Whynes [48] developed a simple, deterministic, model of a CT lung screening regimen, which could potentially be applicable to the UK. The majority of the parameters included in the model had already been established in non-trial settings. The component costs of the modelling were derived from UK government guidance and from published audits, whilst the values for test parameters were derived from clinical studies. The expected health gains as a result of screening were calculated by combining published survival data for screened and unscreened cohorts with data from Life Tables. In order to estimate the most probable costs, conservative estimates were used, which would result in making screening appear less, rather than more, cost effective. This modelling provided an indication of the cost effectiveness of lung cancer screening in the UK. The incremental cost effectiveness ratio of a single screen amongst a high-risk male population was calculated to be around £14,000 per quality-adjusted life year gained.

The cost effectiveness of screening is a function of disease prevalence. With a higher prevalence in the target population, more cases will be detected and more health gains will accrue for the same cost of screening [49]. A lung cancer screening programme which utilises a stringent risk prediction criterion for selection of the population will record a greater number of significant findings per person screened, and a lower ICER, than one with less strict risk prediction criteria. Thus the value of assessing the correct risk prediction programme for the population under investigation is extremely important as this will have a major bearing on the overall cost of the screening programme.

11. Frequency of Screening (Amber)

The USPSTF has advocated that screening should be undertaken annually from 55 years of age to 80 years of age in a pre-specified group of individuals as indicated earlier in the review. However we do now have an opportunity to consider if this is appropriate taking into consideration the potential psychosocial harms, long term accumulation of radiation exposure and cost. This concept has been modeled by Duffy et al [50] and clearly there are pros and cons in taking a less frequent approach

ie, biennial screening. To date the evidence base for low-dose CT screening for lung cancer pertains almost entirely to annual screening. Duffy and colleagues used the currently published data on lung cancer screening data from NLST and UKLS and natural history parameters to estimate the likely effects of annual and biennial screening programmes in different risk populations, in terms of deaths prevented as well as the human costs and included screening episodes, further investigation rates and overdiagnosis.

The annual screening modelling with the UKLS eligibility criteria was estimated to result in 956 lung cancer deaths prevented and 457 over-diagnosed cancers from 330,000 screening episodes. However, the biennial screening modelling would result in 802 lung cancer deaths prevented and 383 over-diagnosed cancers for 180,000 screening episodes. These predictions do suggest that the intervention effect could justify the human costs.

The NELSON authors calculated the probabilities of developing lung cancer over a two year period, stratified by nodule characteristics. They reported that the 2-year lung cancer probability for all included participants was 1·3%, whilst participants without any pulmonary nodule in rounds one and two had a lung cancer probability of 0·4%. In all participants with CT-detected nodules, lung cancer probability was 2.5%, but participants' probabilities were dependent on nodule volume, diameter and volume doubling time.

It is of note that more than half of the participants in the NELSON trial, no pulmonary nodules were detected. Their 2-year probability of developing lung cancer was 0·4%, which suggests that a screening interval of at least 2 years might be safe to apply in these individuals.

Thus there is a potential benefit in considering biennial screening after two years of negative scans and justifies further empirical research, but can only be scored as 'amber ' at this time.

Final recommendations – for planning and monitoring a future managing screening programme

This review has focused on the evidence for implementing lung cancer screening at this time in Europe and thus dealt with the twelve major decision points in this process, however, any future decision will naturally have to include smoking cessation programmes and how they are incorporated, which has to be categorized as 'Amber' at this time, as this will increase the cost effectiveness of the intervention

There is considerable optimism around LDCT screening; however there will be difficult decisions around the overall cost.

The evidence reviewed does point towards an annual screen, in the age group 60 to 74 years, based on risk assessment and with a nodule cut-off in the region of 80-100mm^3. However there is still uncertainty as to most effective method when engaging the hard to reach community, this has been categorized as "Red'. There is good evidence that once a 10mm diameter CT detected nodule is referred to a centre of excellence, there are currently high standard NICE guideline for both the work-up and treatment of these nodules. To date we do not have good mortality data in Europe, however this most likely will be available within the next 12 months from NELSON and in the UK we should then also have the benefit of the pooled NELSON and UKLS data. In a similar time frame we should also have a better indication of the cost effectiveness of lung cancer screening in Europe, however both mortality data and cost effectiveness are still categorised in this review as 'Amber'. Finally the decision to undertake yearly screening from 60 to 75 years of age after two negative scans will have to be further validated and thus has been categorised as 'Amber'.

Implementation, we believe, should be via a phased approach and further delay will mean lives lost.

1. O'Dowd EL, McKeever TM, Baldwin DR, Anwar S, Powell HA, Gibson JE, Iyen-Omofoman B, Hubbard RB: **What characteristics of primary care and patients are associated with early death in patients with lung cancer in the UK?** *Thorax* 2015, **70:**161-168.
2. Marteau TM, Mantzari E: **Public health: The case for pay to quit.** *Nature* 2015, **523:**40-41.
3. van der Aalst CM, van den Bergh KA, Willemsen MC, de Koning HJ, van Klaveren RJ: **Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial.** *Thorax* 2010, **65:**600-605.
4. Land SR, Marcus PM: **Cancer screening and diagnosis: opportunities for smoking cessation intervention.** *J Clin Oncol* 2015, **33:**1631-1632.
5. Aberle DR, DeMello S, Berg CD, Black WC, Brewer B, Church TR, Clingan KL, Duan F, Fagerstrom RM, Gareen IF, et al: **Results of the two incidence screenings in the National Lung Screening Trial.** *N Engl J Med* 2013, **369:**920-931.
6. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, J.D. S: **Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening.** *N Engl J Med* 2011.
7. Field JK, Smith RA, Aberle DR, Oudkerk M, Baldwin DR, Yankelevitz D, Pedersen JH, Swanson SJ, Travis WD, Wisbuba, II, et al: **International Association for the Study of Lung Cancer Computed Tomography Screening Workshop 2011 report.** *J Thorac Oncol* 2012, **7:**10-19.
8. Field JK, Hansell DM, Duffy SW, Baldwin DR: **CT screening for lung cancer: countdown to implementation.** *Lancet Oncol* 2013, **14:**e591-600.
9. Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, Zakher B, Fu R, Slatore CG: **Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive services task force recommendation.** *Ann Intern Med* 2013, **159:**411-420.
10. Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, Zakher B, Fu R, Slatore CG: **Screening for lung cancer with low-dose computed tomography: a systematic review to update the u.s. Preventive services task force recommendation.** *Ann Intern Med* 2013, **159:**411-420.
11. Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, Silvestri GA, Chaturvedi AK, Katki HA: **Targeting of low-dose CT screening according to the risk of lung-cancer death.** *N Engl J Med* 2013, **369:**245-254.

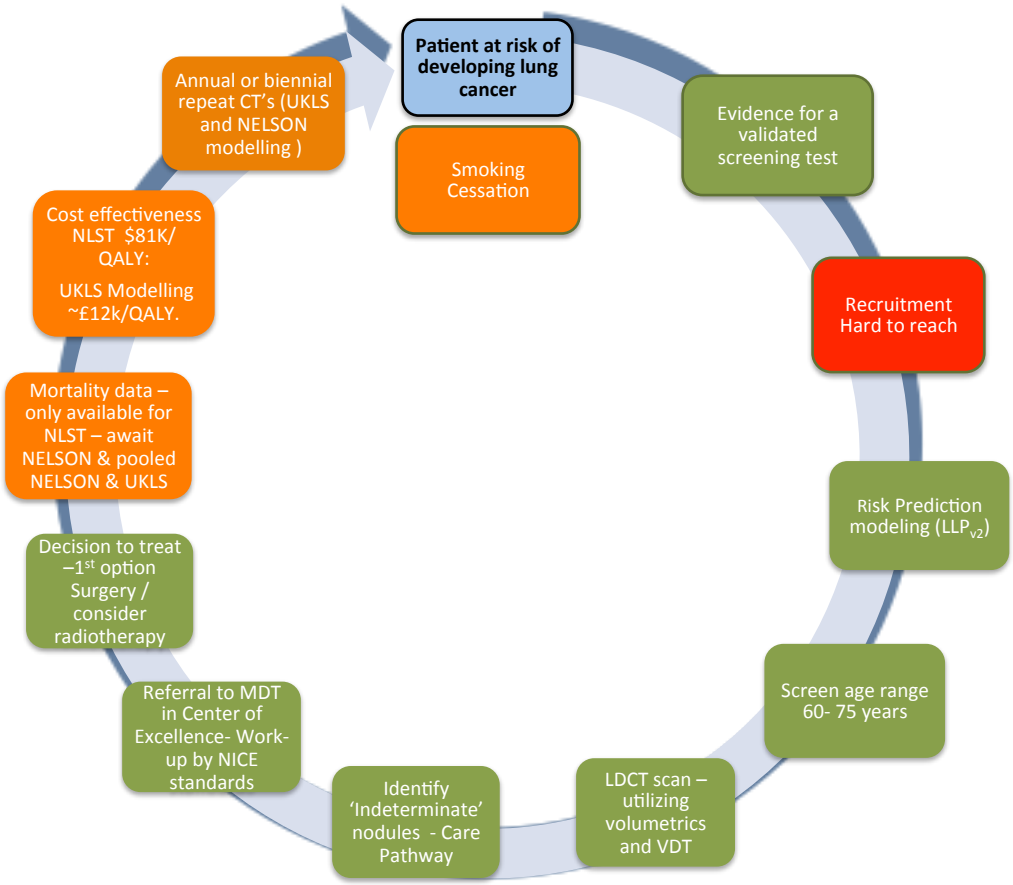
12. Tammemagi MC, Church TR, Hocking WG, Silvestri GA, Kvale PA, Riley TL, Commins J, Berg CD: **Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts.** *PLoS Med* 2014, **11:**e1001764.
13. Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK: **UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer.** *Thorax* 2011, **66:**308-313.
14. Cassidy A, Myles JP, van Tongeren M, Page RD, Liloglou T, Duffy SW, Field JK: **The LLP risk model: an individual risk prediction model for lung cancer.** *Br J Cancer* 2008, **98:**270-276.
15. McRonald FE, Yadegarfar G, Baldwin DR, Devaraj A, Brain KE, Eisen T, Holemans JA, Ledson M, Screaton N, Rintoul RC, et al: **The UK Lung Screen (UKLS): demographic profile of first 88,897 approaches provides recommendations for population screening.** *Cancer Prev Res (Phila)* 2014, **7:**362-371.
16. Field JK, Devaraj A, Baldwin DR, Holemans J, Screaton N, Ledson M, Rintoul RC, Nair A, Gosney JR, Rassl D, et al: **UK lung Cancer Screening trial (UKLS): Prevalence data at baseline.** *Lung Cancer* 2014.
17. 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.
18. 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.
19. Horeweg N, van der Aalst CM, Thunnissen E, Nackaerts K, Weenink C, Groen HJ, Lammers JW, Aerts JG, Scholten ET, van Rosmalen J, et al: **Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial.** *Am J Respir Crit Care Med* 2013, **187:**848-854.
20. Mettler FA, Jr., Huda W, Yoshizumi TT, Mahesh M: **Effective doses in radiology and diagnostic nuclear medicine: a catalog.** *Radiology* 2008, **248:**254-263.
21. Van't Westeinde SC, van Klaveren RJ: **Screening and early detection of lung cancer.** *Cancer J* 2011, **17:**3-10.
22. Heuvelmans MA, Oudkerk M, de Bock GH, de Koning HJ, Xie X, van Ooijen PM, Greuter MJ, de Jong PA, Groen HJ, Vliegenthart R: **Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals.** *Eur Radiol* 2013, **23:**1836-1845.
23. Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers JW, Nackaerts K, Vliegenthart R, Ten Haaf K, Yousaf-Khan UA, et al: **Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers.** *Lancet Oncol* 2014.
24. Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, Franks K, Gleeson F, Graham R, Malhotra P, et al: **British Thoracic Society**

guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015, **70 Suppl 2:**ii1-ii54.
25. 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.
26. Horeweg N, van Rosmalen J, Heuvelmans MA, van der Aalst CM, Vliegenthart R, Scholten ET, Ten Haaf K, Nackaerts K, Lammers JW, Weenink C, et al: **Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening.** *Lancet Oncol* 2014.
27. Horeweg N, van der Aalst CM, Vliegenthart R, Zhao Y, Xie X, Scholten ET, Mali W, Thunnissen E, Weenink C, Groen HJ, et al: **Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial.** *Eur Respir J* 2013, **42:**1659-1667.
28. Herder GJ, van Tinteren H, Golding RP, Kostense PJ, Comans EF, Smit EF, Hoekstra OS: **Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography.** *Chest* 2005, **128:**2490-2496.
29. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, Licker M, Ferguson MK, Faivre-Finn C, Huber RM, et al: **ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy).** *Eur Respir J* 2009, **34:**17-41.
30. Lim E, Baldwin D, Beckles M, Duffy J, Entwisle J, Faivre-Finn C, Kerr K, Macfie A, McGuigan J, Padley S, et al: **Guidelines on the radical management of patients with lung cancer.** *Thorax* 2010, **65 Suppl 3:**iii1-27.
31. Okami J, Ito Y, Higashiyama M, Nakayama T, Tokunaga T, Maeda J, Kodama K: **Sublobar resection provides an equivalent survival after lobectomy in elderly patients with early lung cancer.** *Ann Thorac Surg* 2010, **90:**1651-1656.
32. Billmeier SE, Ayanian JZ, Zaslavsky AM, Nerenz DR, Jaklitsch MT, Rogers SO: **Predictors and outcomes of limited resection for early-stage non-small cell lung cancer.** *J Natl Cancer Inst* 2011, **103:**1621-1629.
33. Schuchert MJ, Abbas G, Awais O, Pennathur A, Nason KS, Wilson DO, Siegfried JM, Luketich JD, Landreneau RJ: **Anatomic segmentectomy for the solitary pulmonary nodule and early-stage lung cancer.** *Ann Thorac Surg* 2012, **93:**1780-1785; discussion 1786-1787.
34. Bao F, Ye P, Yang Y, Wang L, Zhang C, Lv X, Hu J: **Segmentectomy or lobectomy for early stage lung cancer: a meta-analysis.** *Eur J Cardiothorac Surg* 2014, **46:**1-7.
35. Verstegen N, Oosterhuis J, Palma D, Rodrigues G, Lagerwaard F, van der Elst A, Mollema R, van Tets W, Warner A, Joosten J: **Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis.** *Ann Oncol* 2013, **24:**1543-1548.
36. Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, Dossing M, Hansen H, Kofoed KF, Larsen KR, et al: **CT screening for lung**

cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax* 2012, **67:**296-301.
37. Infante M, Cavuto S, Lutman F, Brambilla G, Chiesa G, Ceresoli G, Passera E, Angeli E, Chiarenza M, Aranzulla G, et al: **A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial.** *Am J Respir Crit Care Med* 2009, **180:**445-453.
38. Pastorino U, Rossi M, Rosato V, Marchiano A, Sverzellati N, Morosi C, Fabbri A, Galeone C, Negri E, Sozzi G, et al: **Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial.** *Eur J Cancer Prev* 2012, **21:**308-315.
39. 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.** *New England Journal of Medicine* 2009, **361:**2221-2229.
40. Xu DM, Gietema H, de Koning H, Vernhout R, Nackaerts K, Prokop M, Weenink C, Lammers JW, Groen H, Oudkerk M, van Klaveren R: **Nodule management protocol of the NELSON randomised lung cancer screening trial.** *Lung Cancer* 2006, **54:**177-184.
41. van Iersel CA, de Koning HJ, Draisma G, Mali WP, Scholten ET, Nackaerts K, Prokop M, Habbema JD, Oudkerk M, van Klaveren RJ: **Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON).** *Int J Cancer* 2007, **120:**868-874.
42. Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, Passera E, Angeli E, Chiarenza M, Aranzulla G, et al: **A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial.** *American Journal of Respiratory & Critical Care Medicine* 2009, **180:**445-453.
43. Pastorino U, Rossi M, Rosato V, Marchiano A, Sverzellati N, Morosi C, Fabbri A, Galeone C, Negri E, Sozzi G, et al: **Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial.** *European Journal of Cancer Prevention* 2012, **21:**308-315.
44. Field JK: **Perspective: The screening imperative.** *Nature* 2014, **513:**S7.
45. National Institute for Health and Clinical Excellence: *Guide to the methods of technology appraisal.* London: NICE; 2008.
46. 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.
47. Pyenson BS, Henschke CI, Yankelevitz DF, Yip R, Dec E: **Offering lung cancer screening to high-risk medicare beneficiaries saves lives and is cost-effective: an actuarial analysis.** *Am Health Drug Benefits* 2014, **7:**272-282.
48. Whynes DK: **Could CT screening for lung cancer ever be cost effective in the United Kingdom ?** *Cost Eff Resour Alloc* 2008, **6:**5.

49. Whynes DK: **Could CT screening for lung cancer ever be cost effective in the United Kingdom ?** *Cost Effectiveness and Resource Allocation* 2008, **6:**5.
50. Duffy SW, Field JK, Allgood PC, Seigneurin A: **Translation of research results to simple estimates of the likely effect of a lung cancer screening programme in the United Kingdom.** *Br J Cancer* 2014, **110:**1834-1840.

Figure 1


Patient at risk of developing lung cancer
Smoking Cessation
Evidence for a validated screening test
Recruitment Hard to reach
Risk Prediction modeling (LLP_{v2})
Screen age range 60- 75 years
LDCT scan – utilizing volumetrics and VDT
Identify 'Indeterminate' nodules - Care Pathway
Referral to MDT in Center of Excellence- Work-up by NICE standards
Decision to treat –1st option Surgery / consider radiotherapy
Mortality data – only available for NLST – await NELSON & pooled NELSON & UKLS
Cost effectiveness NLST $81K/ QALY:
UKLS Modelling ~£12k/QALY.
Annual or biennial repeat CT's (UKLS and NELSON modelling)