UK National Screening Committee

Interim report on the cost-effectiveness of low dose computed tomography (LDCT) screening for lung cancer in high risk individuals

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The UK National Screening Committee secretariat is hosted by The Office for Health Improvement & Disparities.

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The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes. Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

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Plain English summary

The symptoms of lung cancer appear in the later stages of the disease. This is often when people are diagnosed and few treatment options are possible. Diagnosis at an earlier stage helps to achieve better results. If we can identify people with lung cancer before they develop symptoms, it is easier to treat the cancer.

Low dose computed tomography (LDCT) uses X-rays to show images through a person's body, and can show lung cancers. People have lower doses of radiation with LDCT than with a standard CT scan.

Many studies have looked at lung cancer screening for people who have smoked in the past or who are smokers. The studies aimed to find out if screening with LDCT would lead to better health outcomes compared to no screening.

The NHS looks at the value for money when considering new health interventions, such as treatments or tests. This involves comparing the benefits of the intervention with how much it costs. Computer models often help with working this out.

This document describes the updating of an existing model and presents the results. The updated version includes recent data from journals and expert opinions. But an important part of the model remains unchanged because it is very complicated. This means that the results in this report are not yet final.

The partially updated model compares several screening approaches for lung cancer. It suggests that LDCT screening for lung cancer is likely to be cost-effective for the NHS. There is still some uncertainty which will be reduced with the updating of the final part of the computer model. The fully updated model will particularly help compare the cost-effectiveness of different possible version of a LDCT screening programme.

Executive summary

Purpose

This document describes details about the updating of an existing model-based economic evaluation of LDCT screening for lung cancer in the UK. Model parameters have been updated with more recent data, where available, and minor structural changes have been made. This document is an interim report on the updating of the model as updates to the natural history component are on-going, and have not been included here.

Background

During 2020 and 2021, the NIHR and the UK National Screening Committee (NSC) (via Public Health England) commissioned further development of a model-based economic evaluation of LDCT for lung cancer screening (ENaBL, Exeter natural history-based economic model of lung cancer screening). The original model showed cost-effectiveness to be at the margins of what would be considered cost-effective in the NHS based on thresholds used by organisations like the National Institute for Health and Care Excellence (NICE). The update was primarily to incorporate additional evidence (in particular from the NELSON randomised controlled trial, Nederlands–Leuvens Longkanker Screenings Onderzoek, which was published in January 2020) and to address concerns surrounding the natural history model developed for the cost-effectiveness analysis. Among the concerns was that the original natural history model estimated that at diagnosis there are more late stage cancers and fewer early stage cancers than is observed in data from trials and national statistics. This consequently means that lung cancer survival may be underestimated, and that the potential benefits of lung cancer screening may not have been captured.

Due to the number of assumptions to be revisited in addressing these concerns, a completely new natural history model is being developed. However, because this is highly complex, the University of Exeter team have been delayed in their delivery of the updated model. Thus, this report serves as an interim report, which explores the effect of updating parameters within the original model-based economic evaluation. The natural history model used in the original report has not been updated, therefore all criticisms and limitations of this part of the model still remain. Work is on-going to update the natural history model, with the aim of presenting a final report based on the revised natural history model and the updated parameter values as described in this interim report.

Focus

The objective of this interim report is to present model results using updated parameter estimates, where available, in the original ENaBL model. The clinical effectiveness of LDCT screening is not addressed in this report, and readers are referred to the Rapid Review commissioned by the NSC secretariat. This interim report deals only with aspects of clinical effectiveness which impact on the estimation of cost-effectiveness.

Recommendation under review

Screening for lung cancer is not currently recommended in the UK.

Findings

Updates to parameter values and limited revisions to the structure of the discrete event simulation (DES) model have lead to 4 LDCT screening strategies lying on the cost-effectiveness frontier in base case analyses. It is estimated that these LDCT screening strategies would likely be cost-effective compared to no screening at a willingness to pay of £20,000 per quality-adjusted life-year (QALY) gained.
All LDCT screening strategies were estimated to be more effective than no screening, suggesting a QALY gain of 0.006 to 0.0029 per person, depending on the strategy.
However, screening strategies were estimated to be more costly than no screening, with an additional cost ranging from £16 to £126 per person, depending on the strategy.
This change in estimates of cost-effectiveness from the original model(1) is driven by the use of updated parameters, which are based on more appropriate data and assumptions than in the original, and are more likely to favour LDCT screening than no screening.

Recommendations on screening

Given the parameter updates and minor structural changes presented in this interim report, ENaBL estimates that screening for lung cancer with LDCT would likely be considered a cost-effective intervention. However, the natural history model component is completely unchanged from the original report. It is difficult to indicate how the ICERs may change once the new natural history model has been completed. This is because multiple assumptions are being modified from the original model, with varying expected effects on the ICERs. Nevertheless, given that the ICER for the most cost-effective strategy in this

interim report is £1,529 per QALY gained, the updated natural history model component would need to lead to an order of magnitude change for the ICER to get close to the willingness to pay threshold of £20,000 per QALY, as used by organisations like NICE. A final report will be produced when the new natural history component has been completed.

Strengths

Although the interim report does not address all the challenges in the modelling of lung cancer screening, it has greatly improved the quality of the parameters through the collaboration and support of clinical experts in the field.

Limitations

The main limitation to the results presented in this interim report is that the natural history model component is completely unchanged from the original model. As the results show, the number and stage distribution of lung cancer diagnoses are still high for stage IV, and very low for earlier stages. The impact of this on estimates of cost-effectiveness was discussed in early engagement meetings, with agreement that this would underestimate the effectiveness (and cost-effectiveness) of LDCT screening compared to no screening, since the value of screening is to identify cancers at earlier stages than they would present clinically. Thus, it might be assumed that when the updated natural history model is complete, the cost-effectiveness of LDCT will look even more favourable. However, there are other changes to the natural history model that were identified as important in early meetings (see

Table 1), and the impact of these may actually lead to less favourable cost-effectiveness estimates. For instance, incorporating heterogeneity in the progression of pre-clinical lung cancer should lead to better capture of overdiagnosis through screening and fast-growing cancers being more likely to be picked up between screening rounds rather than at screening.
The model does not consider the costs or health impacts of incidental findings from LDCT screening. Thus, any additional benefits unrelated to lung cancer that may arise from LDCT screening have not been incorporated.
The database search for utilities was conducted 12 months ago, so any studies reporting relevant utility data published in the last 12 months has not been considered for this interim report. The final report will include an update of the database searches.

Evidence uncertainties

A recently published review(2) identified 35 cost-effectiveness analyses of LDCT screening for lung cancer published since 2000. LDCT screening was generally found to be more effective and more costly than no screening. Reported ICERs ranged from US$1464 to US$2 million per QALY gained depending on policy question, setting, modeling approach, and evidence used. Four CEAs based in the UK were identified – Whynes(3), Field(4), Hinde(5) and the original EnABL report by Snowsill(1). All evaluated a single LDCT screen versus no screen. ICERs ranged from £8466 per QALY gained(4) to £28,169-£30,821 per QALY gained(1) depending on the eligible population. The results from this interim update analysis of ENaBL produce the most favourable cost-effectiveness estimates for a single LDCT screen in the UK, with an ICER of £1,529 per QALY gained.

It is difficult to predict the magnitude of likely over- or under-estimates of cost-effectiveness from addressing the various issues in the natural history component of ENaBL. Thus, it is important that these are addressed in the new natural history model, so that the best estimate for the cost-effectiveness of LDCT screening for lung cancer in the UK can be obtained, and the relative cost-effectiveness of one strategy to another can be assessed. It is also important to provide a valid model with widespread acceptance which can be used to evaluate modifications to a lung cancer screening programme should it be introduced. Such a model will also be useful to other groups assessing the cost-effectiveness of other approaches to reducing the morbidity and mortality of lung cancer (we have been approached by these groups asking permission to use the model when it is completed).

Introduction and approach

Background

Reasons for updating the original model

In November 2016 researchers at the University of Exeter were commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme to investigate the effectiveness and cost-effectiveness of low-dose computed tomography (LDCT) for lung cancer screening (HTA 14/151/07).
The project was completed in summer 2017 and published December 2018 (1). An independent model-based economic evaluation was undertaken, resulting in ENaBL (Exeter natural history-based economic model of lung cancer screening). It consists of a discrete event simulation (DES) model incorporating a natural history model for lung cancer. Four LDCT screening frequencies were evaluated, in addition to no screening, in 12 different populations defined by age range, and predicted risk of lung cancer. The findings indicated that a single (one-off) LDCT screen could be considered cost-effective at conventional willingness to pay thresholds, but that there was “significant uncertainty about the effects of costs and the magnitude of benefits”(1).
When this work was conducted, long-term follow-up results of the NELSON (Nederlands–Leuvens Longkanker Screenings Onderzoek) randomised controlled trial comparing four rounds of LDCT screening with no screening were still unpublished. Results have subsequently been published, reporting a 24% reduction in lung cancer mortality in men (risk ratio (RR) of 0.76%, 95%CI 0.61, 0.94) associated with LDCT screening(6). A RR of 1.01 (95% confidence interval 0.92, 1.11) was reported for overall mortality in men.
The NIHR and the UK National Screening Committee (NSC) (via Public Health England) commissioned further development of the health technology assessment of LDCT for lung cancer screening to incorporate the additional evidence (primarily from NELSON) and to address concerns surrounding the model developed for the cost-effectiveness analysis. ENaBL used within it a model of the preclinical development of lung cancer so that screening programmes can be simulated which have not been evaluated in clinical studies. This natural history model incorporates the risks of developing preclinical (occult) lung cancer, progression of preclinical lung cancer (through seven lung cancer stages based on American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) 7th edition; IA, IB, IIA, IIB, IIIA, IIIB and IV), and the presentation (symptomatic or incidental) of lung cancer.
External validation of ENaBL has shown that its natural history component results in stage distributions in the presence or absence of screening that are not well matched to the stage distributions observed in LDCT trials and national statistics, with an overestimation of late

stage cancers and underestimation of early stage cancers. This consequently means that lung cancer survival may be underestimated, and that the potential benefits of lung cancer screening may not have been captured.

Process for updating ENaBL

Towards the end of 2020, a number of stakeholder meetings were held between the University of Exeter team, members of the NSC, and clinical and modelling experts to discuss the ENaBL model and prioritise the work involved to update and further develop the model (referred to as the Modelling Task and Finish Group meetings).
Resulting from these consultation meetings, the University of Exeter team proposed to:

1. Re-consider, and update where appropriate, all parameters in the original model.
2. Extend calibration and validation of ENABL.

Based on feedback from the Modelling Task and Finish Group meetings, a number of assumptions to revisit in the natural history model were highlighted and are shown in

Table 1. The aim was to calibrate the natural history model with and without these revised assumptions.

Table 1 Potential revisions to assumptions in the natural history model

ID	Assumption in original ENaBL(1)	Likely alternative assumption	Expected effect of revising assumption
A	No lung cancer mortality without prior diagnosis of lung cancer	A certain proportion of people with preclinical lung cancer in Stage III or IV will die from lung cancer without first being diagnosed	Unclear
B	Equal sensitivity of LDCT screening across preclinical lung cancer stages	Separate sensitivity estimates for preclinical Stage IA versus preclinical Stages IB–IV	Sensitivity may be increased for late stages and lowered for earlier stages; Effect on cost-effectiveness will depend on what proportion of early stage cancers are detected if sensitivity is lowered, and how many early stage cancers would be "overdiagnosed".
C	The hazard function for preclinical disease incidence is dependent only on age and sex [a]	The hazard function for preclinical disease incidence will additionally incorporate information about smoking history [b]	Will marginally benefit annual and biennial screening [c]
D	UICC/AJCC 7th edition staging	UICC/AJCC 8th edition staging, including separating Stage IA into Stage IA1, IA2 and IA3 and merging Stages IIA and IIB into Stage II, Stages IIIA and IIIB into Stage III. Stages IIB and IV to remain as they were.	Will likely benefit screening programmes

AJCC, American Joint Committee on Cancer; ENaBL, Exeter natural history-based economic model of lung cancer screening; UICC, Union for International Cancer Control.

Notes: [a] The existing model specifically assumes that once patients have been selected for having ever smoked (i.e., current or former smokers) they face the same risk of developing preclinical lung cancer for each year of life after controlling for age and sex. This does not mean that all patients will get preclinical lung cancer at the same age – event times in the model are sampled from probability distributions.
[b] This could be, e.g., pack years, comprehensive smoking index (CSI), linear prediction from LLPv2 or other risk prediction tool.
[c] The existing model reverse-engineers a distribution for the LLPv2 risk scores from the modelled lung cancer outcomes within 3 years of the model start, which has the effect of meaning those with higher risk scores are more likely to develop lung cancer within 3 years. However, after 3 years has passed, the probability of a simulated patient developing lung cancer is not affected by their simulated risk score. Revising this assumption would mean that those with higher baseline risk could continue to have elevated lung cancer risk, which would benefit annual and biennial screening programmes in the simulation.

At the beginning of 2021, updating of the health technology assessment of LDCT for lung cancer screening began. During this process, further clinical input was sought, particularly in the re-development of the natural history model. This consisted of multiple meetings and correspondence with clinical experts. As part of this, the appropriateness of additional assumptions in the natural history model were raised. This included heterogeneity associated with lung cancer. This can be partly explained by histology, but also, with the progression and presentation of lung cancers to reflect indolent and fast-growing tumours.

Not accounting for indolent tumours, it is assumed that all cancers identified will impact clinically on a patient, and require some intervention. This may not be the case for some very slow growing cancers where the individual would not have experienced any impacts during their lifetime. Not accounting for these slow-growing cancers could lead to overestimation of the (cost-) effectiveness of LDCT screening compared to no screening. This is because not every cancer identified would have impacted on the individual, as they may die from other causes before the lung cancer has any clinical impact (overdiagnosis). Thus, any intervention would be unnecessary, and incur unnecessary costs and potential impacts on quality of life for the individual.

By not accounting for fast-growing tumours, the model will not adequately estimate the number of interval cancers diagnosed in a screening programme, i.e. cancers diagnosed between screens, that will not have been present at the time of screening. If these cancers are not modelled appropriately, the proportion of screen-detected cancers will likely overestimated, leading to overestimates of the (cost-) effectiveness of LDCT screening compared to no screening.

To account for heterogeneity in the updated natural history model, non-small cell lung cancer (NSCLC, stages I-IV), and small cell lung cancer (SCLC, limited and extensive) were to be modelled separately, with additional heterogeneity parameters.

Reasons for an interim report

Due to the number of assumptions to be revisited, a completely new natural history model is being developed. However, because of the complexity of this, the University of Exeter team have been delayed in their delivery of the updated model. Thus, at the request of the UK NSC, we have prepared this interim report, whereby the effect of updating other parameters within the original model can be explored (Aim 1). Reporting interim, or emerging, findings in this way is a timely contribution to discussion of the UK NSC recommendation on lung cancer screening.

There has been no updating of the natural history model used in the original report, therefore all criticisms and limitations of this part of the model still remain. Importantly, this must be kept in mind when reviewing the cost-effectiveness results presented in the Results section. Work is on-going to update the natural history model, with the aim of subsequently presenting a final report based on the revised natural history model and the updated parameter values as described in this interim report.

Importance of the natural history model

The modelling of screening programmes is not straightforward. Challenges such as lead-time bias (where screening leads to an earlier diagnosis date but does not delay the date of death), length bias (where screening tends to identify the slow-growing cancers, but not rapidly developing cancers) and overdiagnosis and overtreatment (where a tumour is detected by screening and treated, but would have never been clinically relevant to the patient during their lifetime) mean that modelling is necessarily complex to achieve realistic estimates of cost-effectiveness. For instance, if overdiagnosis is not accounted for in a model, all screen-detected cancers are assumed to have clinical implications for the patient (when they may not), and the effectiveness of screening is likely overestimated.

A recent review identified 35 published model-based economic evaluations of LDCT screening for lung cancer, with great variation between cost-effectiveness results and methodological approach(2). The review concluded that the more complex models, simulating individual participants with a natural history component (including ENaBL and MISCAN-Lung), were more likely to appropriately address challenges of modelling screening programmes.

The natural history component of ENaBL is incredibly important. To model the impact of screening, estimates of what would happen to an individual if they received screening and what would happen if they did not receive screening are needed. To do this appropriately, knowledge of the natural history of lung cancer for that individual is required. Observable data from trials and national statistics/registries, only provide information from the point of diagnosis, whether through screening or through clinical presentation.
To effectively model the impact of screening, need to know:

- Whether individual has cancer at the start of the screening programme
- The probably of developing cancer throughout the screening programme
- How quickly pre-clinical cancer will progress
- The probably that pre-clinical cancer will be identified through screening
- The probably that pre-clinical cancer will be identified clinically (in the absence of screening)
- The probability of dying from undiagnosed lung cancer (very rare)

The aim of the natural history model is to estimate the risk of these unobservable events.

The ENaBL model is calibrated to the National Lung Screening Trial (NLST) data, meaning that values and distributions for model parameters are selected with the intention that the model will produce realistic outputs.

A measure of the performance of the natural history model (validation) is whether it produces expected outputs when compared with real-world data. In this case, whether the model produces the expected number of lung cancer diagnoses and stage distributions at diagnosis (through screening and no screening). As

Table 2 demonstrates, ENaBL overestimates the proportion of screen-detected lung cancers diagnosed at stage IV, while underestimating screen-detected cancers diagnosed at earlier stages compared to observed data.

Table 2. Stage distributions for screen-detected lung cancers estimated from ENaBL and from observed data

Source	Strategy	Stage						
		IA	IB	IIA	IIB	IIIA	IIIB	IV
ENaBL(1) Estimates taken directly from model	No screening*	7%	2%	2%	1%	6%	4%	77%
	Single	19%	4%	4%	4%	4%	2%	63%
	Triple	22%	5%	4%	4%	4%	2%	60%
	Annual	38%	7%	5%	5%	6%	2%	38%
	Biennial	28%	5%	4%	5%	7%	3%	47%
NLCA(7)	Data for England, 2019 and 2020*	16%	6%	2%	6%	12%	10%**	48%
Liverpool HLP(8)	Single	64%		12%		24%		0%
Manchester LHC pilot(9, 10)	2 rounds	68%		12%		9%		11%
West London LCS pilot(11)	Single	58.6%		3.4%		20.7%		17.2%
UKLS(12)	No screening	14.5%	7.3%	7.3%	3.6%	7.3%	10.9%	49.1%
UKLS(12)	Single	52.4%	11.9%	16.7%	2.4%	11.9%	0%	4.8%
NELSON(6)	No screening	6.9%	6.6%	4.3%	5.6%	14.1%	11.2%	45.7%
NELSON(13)	4 rounds	62%	7%	5%	3%	13%	4%	6%
NLST*(14, 15)**	3 rounds	52%	11%	4%	3%	9%	8%	13%

*Includes any diagnosed lung cancers; **stages IIIB and IIIC combined; ***data for the comparator for NLST are not shown as this was chest x-ray.
ENaBL, Exeter natural history-based economic model of lung cancer screening; HLP, Healthy Lung Programme; LCS, lung cancer screening; LHC, lung health check; NELSON, Nederlands–Leuvens Longkanker Screenings Onderzoek; NLCA, National Lung Cancer Audit; NLST, National Lung Screening Trial; UKLS, UK Lung Cancer Screening

This inconsistency is likely to lead to the model underestimating the effectiveness of LDCT screening, since observed data indicate more screen-detected cancers are diagnosed at earlier stages. However, the extent to which this would underestimate effectiveness is unclear, as even in the absence of screening, ENaBL is estimating much higher proportions of cancers diagnosed at stage IV than national data suggest (see

Table 2).

Linked to this is the estimation of the sensitivity of LDCT screening. This is also an output from ENaBL, and is constant across stages. As noted in Table 1, it is another aspect of the natural history model being revised, so that stage-specific sensitivity estimates are obtained. This may go some way to address the issue of overestimation of cancers diagnosed at stage IV, and give the model more face validity.

However, there is also the issue of heterogeneity in the modelled progression and presentation of lung cancer. As stated above, not adequately addressing this issue could lead to a model that over-estimates the (cost-) effectiveness of LDCT screening. It is difficult to predict the magnitude of likely over- or under-estimates of cost-effectiveness from addressing these various issues. Thus, it is important, that these are addressed in the new natural history model, so that the best estimate for the cost-effectiveness of LDCT screening for lung cancer in the UK can be obtained.

Objectives

The objective of this interim report is to present model results using updated parameter estimates, where relevant, as applied to the original ENaBL model. The clinical effectiveness of LDCT screening is not addressed in this report, and readers are referred to the Rapid Review up-date commissioned by the UK NSC secretariat. This interim report only deals with aspects of effectiveness which impact on the estimation of cost-effectiveness.

The emphasis of this report is on the change in estimates of cost-effectiveness from the original report to this interim report. The relative cost-effectiveness of the different screening strategies has received less attention.

Methods

Decision problem

For this interim report, no changes were made to the decision problem evaluated in the original report(1): to evaluate the cost-effectiveness of 48 LDCT screening strategies (defined by screening frequency and characteristics of the population) and a strategy of no LDCT screening, in a population at high-risk of lung cancer in the UK.

Modelling approach

Population

Those eligible for LDCT screening are assumed to be individuals aged 55-80 years with a history of smoking (current or former). As in the original model, only those individuals with a risk of lung cancer above a specified threshold as calculated by version 2 of the Liverpool Lung Project lung cancer risk prediction model (LLPv2)(16) (3%, 4% or 5%), were invited for screening.
It is further assumed that only those individuals with performance score (PS) 0-2 would take-up the offer of screening. This is based on data from Crosbie 2019(9) where only 1.5% of participants accepting LDCT screening in the Manchester Lung Health Check (LHC) pilot had a PS >2.

Setting and location

As in the original report, the evaluation is based in the NHS in the UK.

Screening programmes

For this interim report, no changes were made to the decision problem evaluated in the original report(1). Four screen strategies were modelled, and compared to a strategy of no LDCT screening:

- A single, one-off LDCT screen (as in the protocol for the UK Lung Cancer Screening (UKLS) trial(4))
- Triple LDCT screening – 3 consecutive annual screens (as in the protocol for the NLST(14))
- Annual LDCT screening (as recommended by the US Preventative Services Task Force (USPSTF)(17))
- Biennial LDCT screening

In addition to screening frequency, strategies were evaluated assuming screening was offered at different lung cancer risk thresholds (as described above), and different age ranges for individuals. Lower age limits were assumed 55 or 60 years old, with upper age limits of 75 or 80 years old. Thus, there were 48 distinct LDCT screening strategies evaluated and compared with no screening.

Perspective, time horizon and discounting

The model perspective was that of the NHS and Personal Social Services. The direct effects of individuals contacted through the screening programme were included.

A life-time horizon was taken, with most simulated individuals having died before age 100. Costs and health outcomes both discounted at 3.5% per annum(18).

Analysis method

Analysis was conducted as in the original report(1). A cost-utility analysis was undertaken, where the costs and quality-adjusted life years (QALYs) were estimated and compared for each of the 49 strategies using the incremental cost-effectiveness ratio (ICER): the incremental costs divided by incremental QALYs. Strategies that are dominated (i.e. their incremental QALYs are lower and incremental costs higher than one or more other strategies), or extendedly dominated (i.e. their ICER is greater than that of the next more effective strategy) are eliminated, and a cost-effectiveness frontier is created.
For the main analysis, strategies are compared with the next most effective strategy on the cost-effectiveness frontier, and with the no screening strategy. Secondary analyses involved evaluation of the cost-effectiveness of the 4 different LDCT screening frequencies and the no screening strategy, within each of the 12 defined populations (i.e. 3 risk thresholds x 2 lower age limits x 2 upper age limits). Deterministic sensitivity analyses were undertaken to assess i) the impact of increasing and decreasing the value of each parameter in turn, and ii) the influence of specific scenario analyses. A probabilistic sensitivity analysis (PSA) was undertaken where parameter values were sampled from relevant distributions to reflect parameter uncertainty.

Software

As stated in the original report, the DES model was developed in Excel, and the natural history model was developed in R and JAGS(1). Additional analyses for updated parameters were conducted in Stata 16.0 (StataCorp LP, College Station, TX, USA).

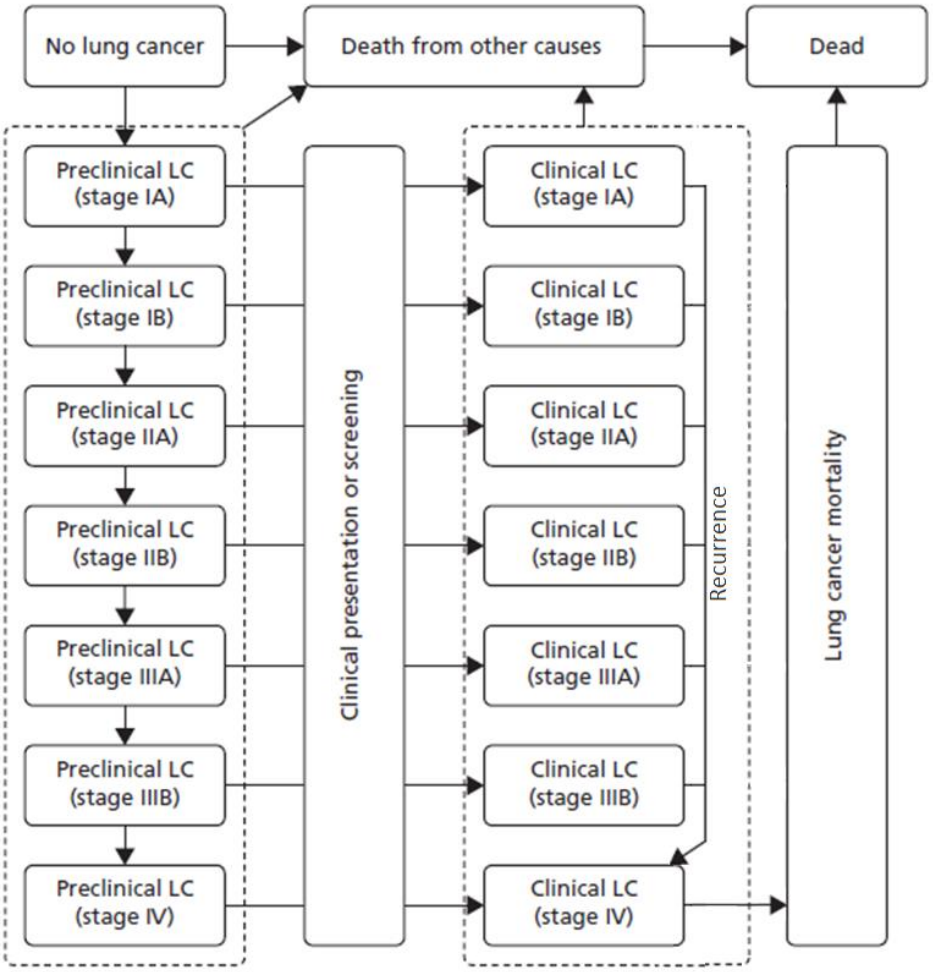
Model structure

No changes have been made to the general modelling approach as described in Snowsill(1).
A cohort of individuals is simulated with a range of baseline characteristics (including age and predicted risk of lung cancer). Each individual is concurrently simulated with four screening intervention arms and the no screening arm. By simulating the individuals concurrently through all arms there is a reduction in stochastic variation. The costs, QALYs and other outcomes for each full programme (combination of population strategy and intervention) are estimated using a decision tree. Costs of administering the screening programme are accumulated through the decision tree, and long-term costs and QALYs are estimated at the leaves of the decision tree by identifying appropriate individuals simulated

in the cohort and assigning them appropriately either to the screening intervention (if they meet all criteria and join the screening programme) or to no screening(1).

The DES modelling involves sampling times to future events according to the current state of the individual (and any relevant history). The earliest of these events is modelled as occurring and the model 'clock' advances to that event. Times to events are then either reduced by the amount the clock has advanced or are resampled (as appropriate) (1).

Figure 1 Model diagram for simulating individuals. LC, lung cancer



To accommodate the revision of cost parameter estimates, a change has been made to the structure of the original DES model (1). In order that newer innovative higher cost drugs are accounted at the right time, recurrent disease is now explicitly modelled. The risk of the new event of 'Recurrence' was added to the decision logic for individuals with clinical lung

cancer stage I to III. Recurrence was not allowed if stage IV was already reached. Allied to this, risk of death from lung cancer in stages I to III was annulled to create the requirement of passage through stage IV lung cancer prior to lung cancer death – unless other cause mortality occurs first. Since recurrence was assumed to signal stage IV lung cancer, existing utility estimates were retained, and the risk/'competing time-to-event' was calculated directly from the natural history model. E.g., Time to recurrence from stage IIB is equal to the sampled time to death from stage IIB minus the sampled time to death from stage IV. See Figure 1.

Model parameters

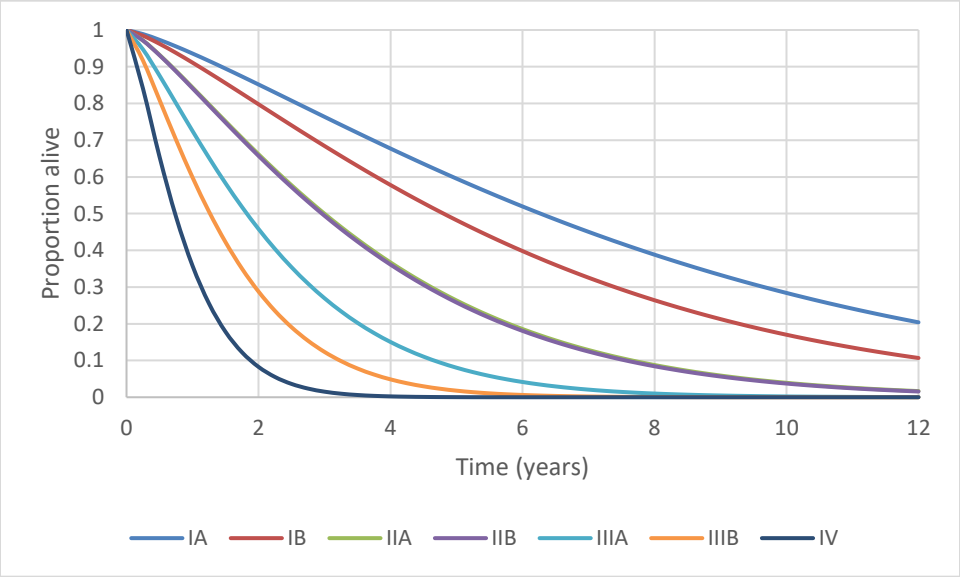
Mortality

Lung cancer mortality

Lung cancer survival was estimated as in the original report(1), according to stage at diagnosis, but with two main updates to the original model. These were that i) Kaplan-Meier curves for NSCLC survival, by stage, were extracted from Goldstraw 2016(19), a more recent publication of the International Association for the Study of Lung Cancer (IASLC) than was used in the original model(20); and ii) survival curves were adjusted to match the one-year survival data obtained from the National Lung Cancer Audit (NLCA) for England 2017-2018 (personal communication David Baldwin), to account for differences in estimated NSCLC survival between the UK and the multiple countries contributing to the IASLC.

Survival data by stage (IA, IB, IIA, IIB, IIIA, IIIB, IV) were extracted from Figure 2A of Goldstraw(19), and a proportional hazards Weibull model was found to be appropriate. In Stata, a weighted linear regression was performed on the log cumulative hazard, with log time and stage as independent variables. As in Snowsill(1), weights were defined as the number of patients diagnosed within each stage multiplied by survival to approximate the number of patients contributing. Each survival curve was then described by a lambda parameter (specific for each stage) and a shared gamma parameter. To adjust these survival curves to reflect the lower survival estimates observed in the UK, the gamma parameter estimated from the weighted regression was assumed for all stages, and the lambda parameters estimated for all stages were adjusted to fit the 1-year survival estimates obtained from the NLCA (Figure 2). Note that in Fig2, the survival curve for stages IIA and IIB are the same. This is because the 1-year survival estimates from NLCA were equivalent for these two stages. This, therefore means that there would be no survival benefit from detecting a cancer in stage IIA, when it would have presented clinically in stage IIB.

Figure 2 Plot of survival curves adjusted to data from the NLCA



Mortality from undiagnosed lung cancer

As in the original model, it is assumed that there is no hazard of dying from lung cancer with undiagnosed lung cancer. However, once a patient is diagnosed their hazard of dying from lung cancer is determined by the stage at which they were diagnosed.

Other cause mortality

No updates were made to the risk of death from other causes.

Effectiveness evidence

Risk prediction

Details on the methods used to estimate lung cancer risk based on LLPv2 are given in the original report (1). No changes have been made to this for the interim report.

Uptake of LDCT screening

In the previous report(1), estimates of screening uptake were taken from UKLS(4). Since the publication of Snowsill(1), regional LDCT lung cancer screening programmes/pilots and trials have been conducted in the UK (Manchester LHC pilot(9), Liverpool Healthy Lung

Programme (HLP)(8), West London lung cancer screening (LCS) pilot(11), Lung Screening Uptake Trial (LSUT)(21)). These have generally taken one of two approaches to inviting individuals to be assessed for their eligibility to partake in LDCT screening for lung cancer. Individuals are identified from GP records and then sent information in the post. They are then invited to either an in-person LHC to assess their eligibility for LDCT screening, or have this assessment via a telephone call.

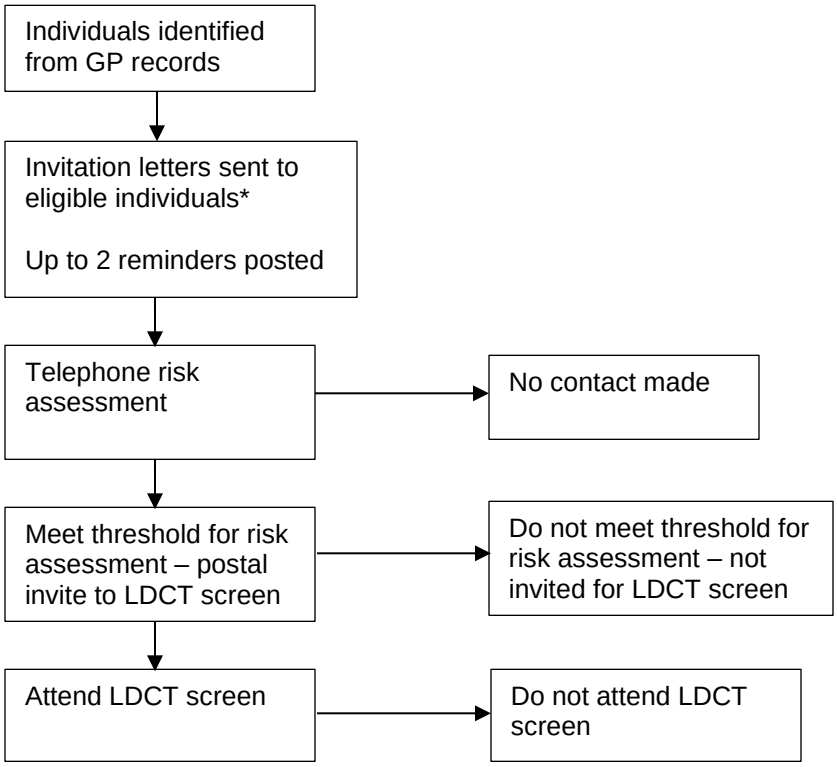
To update the model we used recommendations from the Lung Cancer Screening Pathways Task and Finish Group(22) on the most appropriate pathway to inviting individuals for LDCT screening. The consensus from this group was that a telephone call to assess eligibility would be the most likely way of inviting individuals to take part in screening, should a national programme be commissioned. Thus, in our base case analysis we assume that:

- Potentially eligible individuals are identified from GP records as being 55-80 years old and ever-smokers (including former and current smokers).
- Those identified are sent a letter inviting them to call for a telephone lung cancer risk assessment to evaluate their eligibility to attend a LDCT scan.
- Up to two reminder letters will be sent to individuals to make this call.
- During the telephone call, the risk of lung cancer for that individual is assessed.
- Those found to have a risk above the threshold will be invited to a LDCT scan, with an appointment letter sent to them.

The flow of individuals through the uptake pathway is shown in Figure 3.

There are currently no published uptake results in studies where eligibility for screening is assessed via the telephone. The Yorkshire Lung Screening Trial (YLST)(23) and the SUMMIT study(24) are both using this pathway to identify eligible individuals. The aim of the YLST is to estimate participation in community-based screening, compare risk models for predicting those at high risk for lung cancer, and evaluate clinically-relevant outcomes from LDCT screening(23). We use data from the YLST, kindly provided by Mat Callister and his team (personal communication). Estimates of uptake, and the proportion of reminders sent are presented in Table 3, the resource use and costs associated with this pathway, also taken from the YLST, are presented in Table 8.

Figure 3 Assumed pathway to LDCT screening



*eligibility defined by smoking history and age.

Scenario analyses are conducted assuming uptake rates from the Manchester LHC pilot(9) (see Table 3). The proportion accepting an invite for risk assessment is much lower in the Manchester LHC, than the YLST (28.5% vs 50.8%). This could be explained by the fact that in the Manchester LHC participants had to attend a face-to-face appointment for a risk assessment, while in the YLST the risk assessment was conducted over the telephone. In the Manchester LHC pilot, if individuals were eligible for a LDCT scan, they were offered it on that, or the following, day. While in the YLST, participants made an appointment over the telephone, if eligible, for a future LDCT. The additional costs associated with face-to-face risk assessment in the Manchester LHC are included in the scenario analysis.

It is further assumed that once a participant has entered the screening programme (by attending the first screen), they will participant in any further screening rounds they are invited to attend. Thus, screening compliance is assumed to be 100% for those entering the screening programme. Compared to data available in the published literature, this assumption is likely an over-estimate of screening compliance. Crosbie(10) report that 90.2% of eligible participants returned for the second round of the Manchester LHC pilot, while Horeweg report that in NELSON 97.8% of those eligible for their second screen

attended the second screen and 96.5% of those eligible for the third screen attended their third screen (25).

Table 3. Screening uptake parameters

Parameter	**Base case analysis**		**Scenario analyses**	
	Value	Source	Value	Source
Proportion accepting invite for eligibility risk assessment	50.8%	YLST (personal communication)	28.5%	Manchester LHC pilot(9)
Proportion accepting invite for LDCT scan	**83.6%**	YLST (personal communication)	96.9%	Manchester LHC pilot(9)
Proportion of those approached sent 1st reminders	78.8%	YLST (personal communication)		
Proportion of those approached sent 2nd reminders	**52.7%**	YLST (personal communication)		
Screening compliance	100%	Assumption		

LHC, Lung Health Check; YLST, Yorkshire Lung Screening Trial

LDCT specificity

In the original model, calculation of the specificity of LDCT from UKLS was incorrect. It has now been updated, again based on UKLS(4, 12), assuming that of 1942 participants in the screening arm who did not have a diagnosis of lung cancer within 12 months of LDCT screening, 72 were referred to the MDT for further investigation on the basis of their LDCT scan. Thus, a specificity of (1942-72)/1942 = 0.963 (95%CI 0.953, 0.970) is assumed.

Indeterminate LDCT screening results

Results from a LDCT screen will fall into one of three categories: no follow-up required in this screening round, immediate referral, or an indeterminate result. Those individuals with an indeterminate result require a follow-up LDCT scan(s). If the follow-up LDCT(s) indicates a positive LDCT, individuals will be referred to the MDT for further investigation. If, however,

the follow-up LDCT scan(s) are negative, the individual will re-join any further screening rounds. Based on the UKLS, it is assumed follow-up of an indeterminate LDCT scan would involve a repeat LDCT scan at 3 and at 12 months later, or only at 12 month later(4).

In the original model(1), data on the number of additional LDCT scans were taken from the UKLS where 47% of the sample were defined as having an indeterminate LDCT scan(4): 23% having a 3 month and 12 month scan, and 24% having a 12 month follow-up scan (Table 4). In 2015 the British Thoracic Society (BTS) updated their nodule management guidelines(26). To reflect these updates in the current model, data from UKLS(4) are used but as individuals would have gone through the new BTS guidelines (personal communication from David Baldwin, see Table 4).

Table 4 Proportion of participants having an indeterminant LDCT screening result

Source	% referred immediately	% having 3 and 12 month follow-up LDCT scan	% having 12 month follow-up LDCT scan only	% having no follow-up	Source
UKLS	3.2% 64/1994	23.7% 472/1994	24% 479/1994	49.1% 979/1994	Field(4)
UKLS (as applied to 2015 BTS nodule management guidance)	6%	12%	2%	80%	Field(4) and personal communication [David Baldwin]
Liverpool HLP	9%			81%	Ghimire (8)
Manchester LHC pilot, 1st round	4.7%	12.7%	Only 3 month follow-up scans given	82.6%	Crosbie (9)
Manchester LHC pilot, 2nd round	2%	6%	Only 3 month follow-up scans given	92%	Crosbie (10)
West London LCS pilot	1.7%	14.2%*		84.1%	Bartlett(11)

*14.2% represents the proportion of participants either having LDCT scans at 6 weeks, 3 months, 9 months and/or 12 months, or PET-CT scan.
BTS, British Thoracic Society; HLP, Healthy Lung Programme; LCS, lung cancer screening; LHC, Lung Health Check; NA, not appropriate; UKLS, UK Lung Cancer Screening;

These updated estimates suggest 14% have indeterminate LDCT results, a much lower proportion than assumed in the original model(1). Published data from the Liverpool HLP(8), Manchester LHC pilot(9) and West London LCS pilot(11) are fairly consistent with this (see Table 4 above).

In the interim report, it is assumed that for the annual and triple LDCT screening strategy, individuals requiring a follow-up LDCT scan at 12 months would just re-enter the screening programme in the following year. It is however assumed that for the final screen of the annual or triple screen strategies, individuals may be invited to attend a LDCT 12 months later. Thus, for the base case analysis the proportion of individuals having an indeterminate LDCT screening result, and therefore incurring the additional costs of one or more follow-up LDCT scans, are as given in Table 5.

Table 5 Assumptions on the proportion of individuals receiving a LDCT screen who have an indeterminant LDCT scan result for each modelled screening frequency

Frequency of LDCT screening strategy	% having 3 month follow-up LDCT scan	% having 12 month follow-up LDCT scan
Base case		
Single (one-off)	12%	2%
Annual		NA – re-enter screening
Biennial		2%
Triple – 1st and 2nd rounds		NA – re-enter screening
Triple – 3rd round		2%
Scenario analysis		
Single	0%	14%
Annual		NA – re-enter screening
Biennial		14%
Triple – 1st and 2nd round		NA – re-enter screening
Triple – 3rd round		14%

Based on data from UKLS(4) and personal communication (David Baldwin).

Impact on survival

As with the original model, the approach taken leads to a reduction in lung cancer mortality in terms of a stage shift at diagnosis, with those diagnosed via screening likely to be diagnosed at an earlier stage than if clinically presented.

Health-related preference-based outcomes

EQ-5D is the preferred method to measure health-related quality of life (HRQoL), with the UK time trade-off value set from a sample of the general population the preferred valuation. As in the original model(1), dis-utilities were sought for NSCLC stages I, II, III and IV, and screen-related events. A database search used in the original report was updated (in Feb 2021) Inclusion criteria were as in the previous report: primary studies using EQ-5D to measure HRQoL in patients with lung cancer (unless those patients were experiencing specific adverse events or symptoms), and systematic reviews of EQ-5D in patients with lung cancer. One reviewer screened all titles, abstracts and subsequent full-text articles.

We identified 1,063 hits between January 2017 (the date of the previous database searches) and February 2021. Three studies reporting on utility by lung cancer stage and two studies reporting on screening-related utilities were subsequently screened at full-text.

Lung cancer stage

The systematic review and meta-analysis reported by Blom(27) was identified from the update search as being directly relevant in providing EQ-5D utilities for lung cancer stages. In Blom (27), utilities are meta-analysed regardless of the method used to value the utility, and are reported for lung cancer overall or combined in stages I-II and stages III-IV (

Table 6). Among the identified studies in Blom we found none conducted in the UK using the EQ-5D. The most appropriate included study was Tramontano(28) which was used in the original report to inform the lung cancer stages.

The study by Yang(29) is set in Taiwan and includes 1715 patients with lung cancer. EQ-5D values are reported using the Taiwan and the UK tariff, however, the authors report some adjustment of utility values from the Taiwan tariff to limit values between 0 and 1. It is not clear whether the same constraints have been placed on the UK tariff EQ-5D values. Due to this uncertainty and EQ-5D mean estimates being split by age and squamous cell carcinoma (for NSCLC), these values are difficult to apply to our model (

Table 6). Zeng 2020(30) measured EQ-5D using Chinese tariff for just 93 patients with lung cancer, and report mean values for stages I, II, III and IV (

Table 6).

Given the lack of evidence identified in the update searches for EQ-5D utilities by lung cancer stage, there was no reason to change the evidence source used in the original model, Tramontano 2015(28). This US study reported EQ-5D values for stages I, II, III and IV from 2396 individuals with lung cancer (

Table 6).

Table 6 Published EQ-5D values for lung cancer

Study	Participant characteristics	Tariff	Stage/category	Mean EQ-5D
Blom 2020(27) Systematic review	Multiple countries, NSCLC and SCLC, all valuation methods	Mixed	All stages	0.68 (95%CI 0.61, 0.75)
			I-II	0.78 (95%CI 0.70, 0.86)
			III-IV	0.69 (95%CI 0.65, 0.73)
Yang 2019(29)	Taiwan, NSCLC, N=1715	UK	SqC I-IIIA (<65yrs)	0.80 (SE 0.03)
			SqC IIIB-IV (<65 yrs)	0.74 (SE 0.04)
			NSqC I-IIIA (<65 yrs)	0.84 (SE 0.01)
			NSqC IIIB-IV (<65 yrs)	0.77 (SE 0.01)
			SqC I-IIIA (≥65yrs)	0.78 (SE 0.02)
			SqC IIIB-IV (≥65 yrs)	0.61 (SE 0.04)
			NSqC I-IIIA (≥65 yrs)	0.79 (SE 0.01)
			NSqC IIIB-IV (≥65 yrs)	0.72 (SE 0.02)
Zeng(30)	China, Unclear if NSCLC and/or SCLC, N=93	Chinese	I	0.8 to 0.9*
			II	~0.7
			III	~0.6
			IV	0.38 to 0.57*
Tramontano (28)	US, N=2396	US	I	0.81 (SD 0.17)
			II	0.77 (SD 0.17)
			III	0.77 (SD 0.18)
			IV	0.76 (SD 0.19)

* depending on whether used EQ-%D-3L or EQ-5D-5L;
NSCLC, non-small cell lung cancer; NSqC, non-squamous cell; SCLC, small cell lung cancer; SqC, squamous cell

Although there are many differences in the studies reporting EQ-5D utilities, the values assumed from Tramontano(28) are somewhat consistent with those in Blom(27) (although Tramontano was the largest study in that meta-analysis) and Yang 2020(29). While estimates from Zeng(30) cover a much greater range than those assumed from Tramontano: 0.9 – 0.4 (stage I – stage IV, for EQ-5D-5L), and 0.8 - 0.6 (stage I - stage IV, for EQ-5D-3L).

As in the original model, we assign the utility for the stage at diagnosis for the remainder of the participants life, this is a simplifying assumption. The utilities reported by Tramontano(28) were obtained within 6 months of participants receiving their lung cancer diagnosis. Additional analyses by Tramontano for participants followed up approximately 1 year later show a statistically significant reduction in EQ-5D utility for late stages. In a scenario analysis, the impact of assigning a lower utility to stage IV is assessed (see Table 7).

Assignment of pre-clinical stage utilities

In contrast to clinical disease and unchanged from the original approach, simulants explicitly modelled through the sequence of stages whilst lung cancer remains pre-clinical.

Consequently, utility estimates should not include deterioration associated with stage progression. We have therefore revised the pre-clinical stage II and III estimates to not include the respective decrements versus stage I lung cancer. Since stage IV lung cancer is the 'final' stage the decrement relative to stage I is justified given that no worse living health state can be reached – and the prevalence of clinical symptoms are relatively higher. The original utility assumption was that the diagnosis of lung cancer does not impact the utility experienced at any given stage of disease, but this assertion cannot be implemented since preclinical stages are modelled individually whilst clinical stages are combined through to the end of life.

LDCT screening

We specifically sought utilities related to LDCT screening, and to having a false positive LDCT result for lung cancer, which would include any unnecessary further investigations. To inform utilities related to LDCT screening, two studies were potentially relevant from the update searches: a primary lung cancer screening study in Canada(31), and a systematic review of disutilities for cancer screening(32). The systematic review by Li 2019(32) did not include any new evidence specific to lung cancer screening.

The primary study by Taghizadeh 2019(31) reported EQ-5D from 1237 individuals undergoing LDCT screening using the Canadian tariff. Taghizadeh 2019(31) reported no difference in EQ-5D values at study enrolment, or 1 month and 12 months after receiving the LDCT scan result. For individuals who received a positive LDCT scan result, no differences in EQ-5D values were observed at study enrolment, compared to values 1 month after their positive result, 1 month after additional follow-up LDCT or other tests, and 12 months after enrolment. Separate analyses for those participants found to have false positive LDCT scan results are not reported. As well as measuring EQ-5D, Taghizadeh measured anxiety using the State Trait Anxiety Inventory (STAI)-State anxiety score. The only statistically significant change from baseline reported in Taghizadeh 2019 was for the STAI-State anxiety score at 1 month for all individuals.

Taghizadeh(31) is the only study we are aware of that measures EQ-5D associated with LDCT screening. Based on the EQ-5D data reported in this study, suggesting no disutility associated with a LDCT scan, nor with a positive LDCT scan (including any further investigations), we do not assume any disutilities associated with screening in the base case analysis.

However, in a scenario analysis, to reflect evidence of a change in anxiety score as seen on the anxiety-specific questionnaire used by Taghizadeh(31) ((STAI)-State anxiety score), and other evidence as discussed in the previous report(1), in scenario analyses disutilities are assumed, as in the original model:

- A disutility of 0.01 for a 2 week period associated with a LDCT scan
- A disutility of 0.063 for a 3 month period associated with a false positive LDCT scan result.

The utilities and disutilities assumed in base case and scenario analyses are shown in Table 7.

Table 7 Utilities and dis-utilities assumed in the model

Event	Base case analysis		Scenario analyses	
	Mean (SE) utility	**Source**	**Mean (SE) utility**	**Source**
Stage IA and IB	0.81, 0.006	Tramontano(28)		
Stage IIA and IIB	0.77, 0.011			
Stage IIIA and IIIB	0.77, 0.007			
Stage IV	0.76, 0.008		0.518	Sturza(33)
LDCT screen	0.00, 0.008	Taghizadeh(31)	-0.01 (for 2 weeks)	NELSON(34)
False positive result	0.00, 0.015		-0.063 (for 3 months)	Mazzone(35)

NELSON, Nederlands–Leuvens Longkanker Screenings Onderzoek; SE, standard error

Resource use and costs

Programme administration costs

Two information technology (IT) costs were included in the cost analysis since they are variable and distinct from fixed or transactional costs related to setting in place a programme. The current annual cost of extraction of executable data from primary care IT systems is estimated as £36,000 based on a government contract price for an existing centralised patient index service(36). This was applied as a one-off cost for the identification of all age-eligible ever-smoker individuals for potential participation because in this static population model we are concerned only with a single year intake. Spread over an estimated 13 million ever-smokers in England(37), the per person cost (for the purposes of cost-effectiveness analysis) is under 1p and is therefore negligible. However, the cost of creating and running a dedicated digital database of participants is enduring. This is estimated as £2.06 per subject per year, based on databasing of Abdominal Aortic Aneurysm screening(38). It was assumed that this cost was no longer applicable after death or after the scheduled end of the programme.

The costs per item of resource required for the intended approach to programme recruitment, based on written correspondence and telephone triaging, were obtained audited costs accrued by the YLST (thanks to Professor Matthew Callister, Leeds Teaching Hospital NHS Trust). Pre-invitation letters/notices were sent to all ever-smokers within the entry age criteria of each screening programme design; invitation to participate letters were sent as follow-up to the same group – with reminders to those failing to respond; triage telephone calls - including attempts - were made to the positive subgroup thereof; and screen appointment letters were sent to the further subgroup identified as meeting the programme risk criteria.

Table 8 Unit costs of resources for programme recruitment

Resource	Unit cost (£)
Pre-invitation notice	£0.66
Invitation letter for participation	£0.79
Invitation reminder (as needed*)	£0.84
Telephone triage call	£7.62
Invitation letter for screening appointment	£0.70

*72% received a first reminder; 55% received a second reminder (based on the YLST experience)

LDCT

On the day of the screening the included resources were the LDCT scan itself and the cost of nurse time in support. This was approximated as 15 minutes of band 4 hospital nurse equivalent (unit cost £7.75). LDCT costs was assumed to be the same, whether it be the single one-off screen of the single screening programme design, or the 8th annual screen of the annual screening programme design. The unit cost of this LDCT in the base case was the weighted mean cost of all records in the NHS Reference cost schedule 2019/2020(39). Alternative unit costs, based on the setting of conduct, were examined in scenario analyses. In all cases the resource is collated as HRG RD20A Imaging: Computerised Tomography Scan of One Area, without Contrast, 19 years and over.

Table 9 Unit costing of LDCT

LDCT setting	Unit cost (£)
Weighted all settings (base case)	£77.31
Direct Access	£88.31
Outpatient 1	£91.13
Outpatient 2	£72.47
Other	£94.47

Resource use for false positives

False positives are defined as those individuals referred to the MDT on the basis of LDCT screening results, but who do not receive a diagnosis of lung cancer within 12 months of the LDCT screen. Resource use for these individuals is informed by the UKLS(4) and unit costs were sourced from the NHS Reference cost schedule 2019/2020(39), see Table 10.

Table 10 Resource consumption and unit costs associated with false positive cases

Investigations/treatments received	Proportion of those referred to MDT but not found to have lung cancer (N=72 from UKLS)	Unit cost per intervention
MDT meeting	100%	£116.81
Further CT scan	84.7%	£77.31
Out-patient follow-up	30%	£151.13
PET scan	18%	£665.58
Needle biopsy	9.7%	£724.09
Surgical referral	5.5%	£57.00
EBUS	1.4%	£973.56
Oncology referral	1.4%	£59.50

CT, computed tomography; EBUS, endobronchial ultrasound; MDT, multidisciplinary team; PET, positron emission tomography; UKLS, UK Lung Cancer Screening

Indeterminate cases

These cases were defined by their requirement for further follow-up with subsequent LDCT at 3 or 12 months (see Table 5). For screening programmes with routine subsequent screens at 12 months, the source estimate (of requirement) was adjusted to zero at that timepoint.

Lung cancer costs

As originally, lung cancer care included resources for diagnostic imaging, surgery, radiotherapy, and medical therapeutic intervention. However, the approach to deriving estimates of uptake were revised according to an improved method of micro-costing.
The 2014 Cancer Research UK list of lung cancer resources given in ‘Saving Lives Averting Costs’ (40) was adapted to reflect available resource options for patients diagnosed in 2018 and focussed on consumption by stage at diagnosis for good performers (PS 0-2) aged 55-77. The process of adaptation was by led by Dr David Baldwin with consensus from the Clinical Expert Group for lung cancer, hosted by the Roy Castle Lung Cancer Foundation (previously NHS England 2014 to 2020).
Consumption rates post-diagnosis were adjusted according to survival and applied at the time of event, both improvements of particular relevance to the high costs associated with

recurrence. Separately, ongoing monitoring resources were applied for five years post-diagnosis or until death except for six months after diagnosis and recurrence, to avoid double counting. See Table 10, Table 11 and Table 12.

Table 11 Rate of consumption and unit cost of lung cancer resources by stage at diagnosis - Diagnostics, Surgery and Radiotherapy

Type	Intervention	Unit cost (£)	Diagnosis				Ongoing				Recurrence			
			Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV
Diagnostics and imaging	Chest X-ray	£42	90%	90%	90%	90%	200%	200%	200%	200%	90%	90%	90%	80%
	Contrast enhanced chest, lower neck, and abdomen CT	£115	99%	99%	99%	95%	120%	120%	140%	200%	99%	99%	90%	60%
	PET-CT	£303	80%	80%	80%	15%	5%	5%	5%		30%	30%	5%	15%
	Spirometry	£146	85%	85%	80%	25%	10%	10%			30%	30%		
	T[L]CO test	£130	70%	70%	50%	10%					10%	10%		
	Flexible bronchoscopy alone - no EBUS	£652	10%	10%	10%	18%	10%	10%	10%	5%	10%	10%	10%	5%
	EBUS-guided TBNA plus or minus bronchoscopy	£749	20%	40%	80%	50%	10%	10%	10%	10%	50%	50%	15%	10%
	CT biopsy	£181	60%	40%	5%	30%					15%	30%	5%	5%
Surgery	Elective - Lobectomy, wedge resection, pneumonectomy, segmental resection, sleeve resection	£4,357	67%	65%	18%	2%								
	Emergency - Lobectomy, wedge resection, pneumonectomy, segmental resection, sleeve resection	£6,303	1%	1%	1%						1%	65%	18%	2%
	Airway stents for endobronchial obstruction	£1,515				5%						1%	1%	2%
	Endobronchial debulking	£7,720				5%								2%
Radio-therapy	Intracranial procedures	£3,084				1%								1%
	RT for curative intent (SABR)	£3,999	21%			2%								
	RT for curative intent (non-SABR)	£3,440	2%	23%	10%	2%					4%		10%	
	Palliative RT	£917			14%	60%							14%	60%

EBUS, endobronchial ultrasound; CT, computed tomography; PET-CT, positron emission ultrasound – computed tomography; T[L]CO, transfer factor for carbon monoxide; TBNA, transbronchial needle aspiration; RT, radiotherapy; SABR, stereotactic ablative radiotherapy

Table 12 Rate of consumption and unit costs of lung cancer resources by stage at diagnosis – therapeutic treatment

Type	Intervention	Unit cost (£)	Diagnosis				Recurrence			
			Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV
Chemo-radiotherapy / IO	Curative intent	£5,505			33%	0%	20%	20%		
Chemotherapy	Docetaxel monotherapy	£3,832				4%	4%			4%
	Docetaxel plus nintedanib	£8,743							5%	5%
	Pemetrexed maintenance	£12,576				5%	5%			4%
Chemotherapy doublet	platinum + vinorelbine (adjuvant in stage II)	£1,506		39%	7%	3%	3%			3%
	Gemcitabine + carboplatin	£2,372				4%	4%			4%
	Gemcitabine + cisplatin	£1,844				1%	1%			1%
	Pemetrexed + platinum	£5,869				4%	4%			4%
Immunotherapy	Pembrolizumab	£18,859			10%	14%	14%	10%	14%	14%
	Durvalumab	£32,699			20%			20%		
Chemo-immunotherapy	Pembrolizumab + carbo/cis + gem/pemetrexed	£23,901			15%	28%	28%	28%	28%	
TKI	Gefitinib	£13,788				1%	1%	1%	1%	
	Erlotinib	£3,063			1%	1%	1%	1%	1%	
	Entrectinib	£41,149				1%	1%	1%	1%	
	Crizotinib	£55,090				1%	1%	1%	1%	
	Alectinib	£87,630			1%	1%	1%	1%	1%	
	Osimertinib	£28,451				3%				
	Afatinib	£42,756			1%	1%	1%	1%	1%	1%
	Brigatinib	£55,290			33%	1%	1%	1%	1%	

IO, immunotherapy; TKI, tyrosine kinase inhibitor

Table 13 Summary lung cancer resource costs by stage at diagnosis and type

Cost type	Stage I			Stage II			Stage III			Stage IV		
	Diagnosis	Recurrence	On-going	Diagnosis	Recurrence	On-going	Diagnosis	Recurrence	Ongoing	Diagnosis	Recurrence	On-going
Diagnostics	£933	£766	£392	£1,046	£793	£392	£1,249	£343	£401	£788	£265	£422
Surgery	£2,982	£63		£2,895	£4,112		£847	£1,150		£549	£311	
RT	£909	£138		£791			£472	£472		£730	£581	
Chemo-rad		£1,101			£1,101		£1,817					
CT		£782						£437		£782	£656	
CT doublet		£393		£587			£105			£393	£393	
Immunotherapy		£2,640			£8,426		£8,426	£2,640		£2,640	£2,640	
Chemo-immunotherapy		£6,692			£6,692		£3,585	£6,692		£6,692		
TKI		£2,988			£2,988		£1,334	£2,988		£3,772	£428	
Follow-up	£271	£271		£217	£108		£162	£108		£108	£108	
Total	£5,094	£15,834	£392	£5,537	£24,220	£392	£17,999	£14,831	£401	£16,456	£5,382	£422

CT, computed tomography; Chemo-rad, chemoradiotherapy; TKI, tyrosine kinase inhibitor; RT, radiotherapy

Summary of changes made to original model

Table 14 Summary and justification of updates to original model in the interim report

Aspect of model	Original model(1)	Updated model	Justification
Structure			
Recurrence	Clinical stage progression is implied since costs are informed by stage at diagnosis and utility is adjusted according to the stages remining to be lived.	Recurrence is added as an event, allowing a time-specific attribution of mean costs at recurrence, including the relatively high cost of new TKI and immunotherapy options.	High cost interventions used at progression/recurrence have become a larger proportion of overall disease costs in recent years. Including a recurrence event allows these costs to be included after diagnosis – important in the context of discounting future costs.
Parameters			
Screening uptake parameters	From UKLS(4)	From YLST (personal communication, Mat Callister)	Based on the Pathways Task and Finish group recommendations, likely pathway to screening programme to be through telephone triage (as in YLST) rather than through post questionnaire (as in UKLS). Also, YLST population likely to be more representative than modelled population
Dis-utilities for screening events	Based on EQ-5D VAS results from NELSON(34) and EQ-5D results for chest x-ray screening(35)	Based on EQ-5D results from LDCT screening study(31)	Updated data source more representative of research question
Dis-utilities for stage progression	Clinical stages were assumed to attract the same stage utilities as preclinical stages on the basis that diagnosis would not impact symptom based well-being. Stages attract an increasing disutility relative to stage IA/B. Tramontano(28)	Clinical stages IIA/B and IIIA/B do not attract a disutility relative to Clinical stages IA/B; clinical stage IV retains the relative disutility.	The original assertion is incorrect in practical application since pre-clinical stages are sequential, exclusive and explicit, compared to clinical stages which are combined and indiscernible since each represent utility from diagnosis until stage IV.
Proportion of screened individuals having follow-up LDCT scans for indeterminate results	Based on UKLS(4)	Updated based on UKLS(4) as applied to current BTS nodule management guidance(26)	Updated data more representative of likely screening programme (and consistent with UK LDCT screening pilots/programmes)

Specificity	Based on incorrect data from UKLS	Updated calculation	Correction in calculation of specificity from UKLS. A false positive case is defined as someone referred to the MDT for further investigation but did not receive a diagnosis of lung cancer within the following 12 month period.
Lung cancer mortality	Based on Goldstraw 2007(20)	Goldstraw 2016(19) adjusted for NLCA (personal communication, David Baldwin)	Updated survival estimates published since original model. To reflect reduced survival in UK, survival was adjusted using 1-year survival from NLCA. Updated survival also allows consistency with updated LC treatment costs (see below)
Screening programme costs	Based on invitation and triaging by postal correspondence. Unit costs from ten Haaf(41)	Based on telephone triaging and postal correspondence. Unit costs from YLCT (personal communication, Matthew Callister)	New UK regional evidence has become available to support a telephone triage approach (including uptake and joining rates), and provide health system specific unit cost estimates.
LDCT costs	Based on the unit cost of a direct access Computerised Tomography Scan of one area, without contrast, 19 years and over (HRG RD20A)(42)	Based on a weighted average unit price across all settings (same HRG), using updated NHS reference costs(39)	The preference of expert clinicians consulted as part of the revision of costs was for an 'all-settings' approach because it could not be assumed that the Direct Access setting better described the setting anticipated for LDCTs as part of a national screening programme.
Diagnosis and treatment costs	Based on a two-year costing approach, with index year costs from a UK teaching hospital(43), and second year costs estimated from the index year using a subsequent year ration from database analysis in England(44)	A five-year micro-costing approach which discerns costs at diagnosis from those at recurrence and through follow-up. Consumption is based on the most recent NLCA secondary care estimates for PS 0-2 in the 55-75 year age range.	Clinical expert feedback from workshops supporting the update of this research indicated a likely underestimation of late stage treatment costs due to the emergence new technologies since the time of the original source estimate.

BTS, British Thoracic Society; HRG, healthcare resource group; NELSON, Nederlands–Leuvens Longkanker Screenings Onderzoek; NLCA, National Lung Cancer Audit; MDT, multidisciplinary team; PS, performance status; TKI, tyrosine kinase inhibitor; UKLS, UK Lung Cancer Screening; VAS, visual analogue scale; YLST, Yorkshire Lung Screening Trial;

Results

Naming convention

As in the original report(1), LDCT screening strategies are referred to in terms of: frequency – lower age limit – upper age limit – risk threshold.

Frequency is S for single, T for triple (annual scans for 3 years), A for annual and B for biennial. Lower age limit is either 55 or 60 years old, upper age limit is either 75 or 80 years old, and risk threshold is either 3(%), 4(%) or 5(%).

The screening strategy S-55-75-3 therefore represents a single screen for individuals aged 55-75 years who have a predicted risk of lung cancer of ≥3%.

Base case analyses

Forty-eight hypothetical screening programmes were modelled, as well as a no-screening comparator arm, representing current practice.

Main analysis

The deterministic base case results presented below were conducted by simulating a cohort of 3,000 individuals. Each simulant was created using ten unique but repeatable random numbers by which to sample baseline characteristics, natural history events, and screening outcome. In this way, the same simulants could be used in sensitivity and scenario analyses, except that in univariate sensitivity analyses only the first 1,000 individuals were used.
The different population selection criteria produced a wide range of proportions of smokers joining screening programmes (from 3.6% for 60–75–5% to 12.6% for 55–80–3%), as shown in Table 15. The predominant reasons for ever-smokers not joining screening programmes were not responding to the initial invitation or being of too low predicted risk of lung cancer.

Table 15 Proportion of ever-smokers 55-80 years joining and not joining screening

	Proportion of base population aged 55-80 years (%)				
			Non-joiners		
Population criteria	**Joiner, %**	**Decline, %**	**Risk too low, %**	**No response, %**	**Outside age/ Not invited, %**
No screening	-	-	-	-	100
55-80-3%	12.6	2.5	35.7	49.2	0.0
55-80-4%	8.0	1.6	41.2	49.2	0.0
55-80-5%	5.3	1.0	44.4	49.2	0.0
60-80-3%	12.1	2.4	23.3	36.6	25.7
60-80-4%	7.8	1.5	28.4	36.6	25.7
60-80-5%	5.2	1.0	31.5	36.6	25.7
55-75-3%	10.2	2.0	35.1	45.9	6.8
55-75-4%	5.9	1.2	40.3	45.9	6.8
55-75-5%	3.7	0.7	42.9	45.9	6.8
60-75-3%	9.7	1.9	22.7	33.3	32.4
60-75-4%	5.7	1.1	27.5	33.3	32.4
60-75-5%	3.6	0.7	30.0	33.3	32.4

Cost-effectiveness

Four of the modelled screening strategies were on the cost-effectiveness frontier (i.e., strategies that can give the maximum net monetary benefit (NMB) for at least one choice of the cost-effectiveness threshold) and 'no screening' was also on the frontier (the least costly and least effective option).

Table 16 Base case cost-effectiveness of strategies on the cost-effectiveness frontier (per ever-smoker 55-80 years)

Strategy (ranked by ascending cost)	**Costs (£)**	**QALYs**	**ICER vs No screening (£)**	**Incr. Costs vs next least costly (£)**	**Incr. QALYs vs next least costly**	**Full ICER (£)**
No screening	£3,463	8.511	-	-	-	-
S-55-75-4%	£3,479	8.522	£1,529	£17	0.011	£1,529
T-55-75-4%	£3,494	8.526	£2,179	£14	0.003	£4,313
A-55-75-3%	£3,550	8.537	£3,336	£56	0.012	£4,722
A-55-80-3%	£3,588	8.540	£4,385	£39	0.003	£14,984

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life year

Table 16 presents the base case incremental cost-effectiveness results. Only strategies on the cost-effectiveness frontier are shown. All strategies were predicted to lead to health benefits (vs. no screening), ranging from 0.006 to 0.0029 QALYs per person; and additional costs (vs. no screening), ranging from £16 to £126. Although such gains would not

generally be considered significant, these gains are concentrated in people who join the screening programme (ranging from 3.6% to 12.6% of the population) and are diagnosed with lung cancer at an earlier stage and, therefore, receive more substantial health benefits. The comparison is presented in the next table (Table 17).

Table 17 Relative attainment of benefit between joiners and non-joiners for strategies on the cost-effectiveness frontier

Incremental benefit Vs No screening	**Frontier strategy**			
	S-55-75-4%	**T-55-75-4%**	**A-55-75-3%**	**A-55-80-3%**
Average programme joiners				
Life-years gained	0.371	0.484	0.534	0.465
QALYs gained	0.185	0.242	0.256	0.227
Average ever-smokers 55-80				
Life-years gained	0.022	0.028	0.054	0.059
QALYs gained	0.011	0.014	0.026	0.029

QALYs, quality-adjusted life year

Figure 4 presents the cost-effectiveness plane with all screening strategies measured against No screening. There is a pattern of increasing cost and QALYs as the number of screens in the programme design increases. The same pattern is observed in respect to lung cancer risk: lowering the threshold leads to increasing costs and QALYs. The impact of entry age range on costs and QALYs is less clear. Figure 5 shows only the strategies forming the cost-effectiveness frontier (solid line). Table 18 is a summary of selected clinical outcomes for those screening strategies on the cost-effectiveness frontier.

Figure 4 Cost-effectiveness plane for base-case results (all strategies)

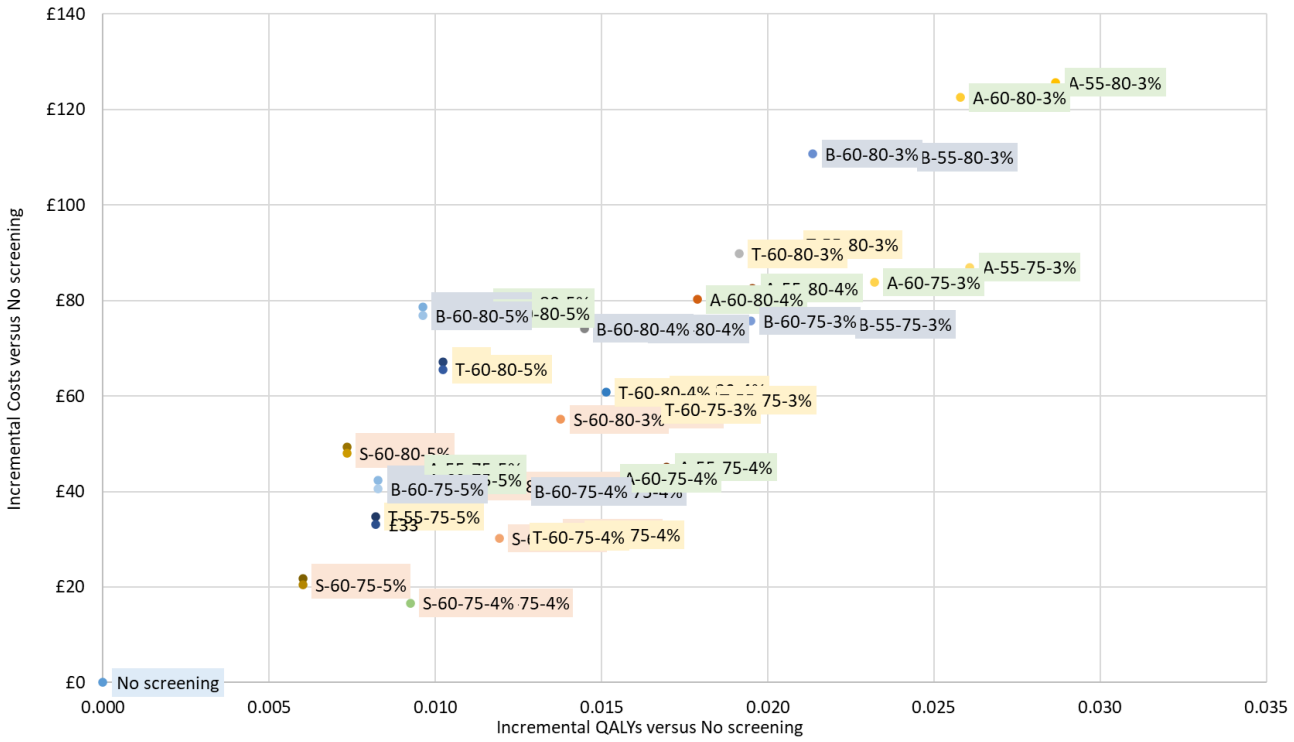


Figure 5 Cost-effectiveness frontier for base-case results

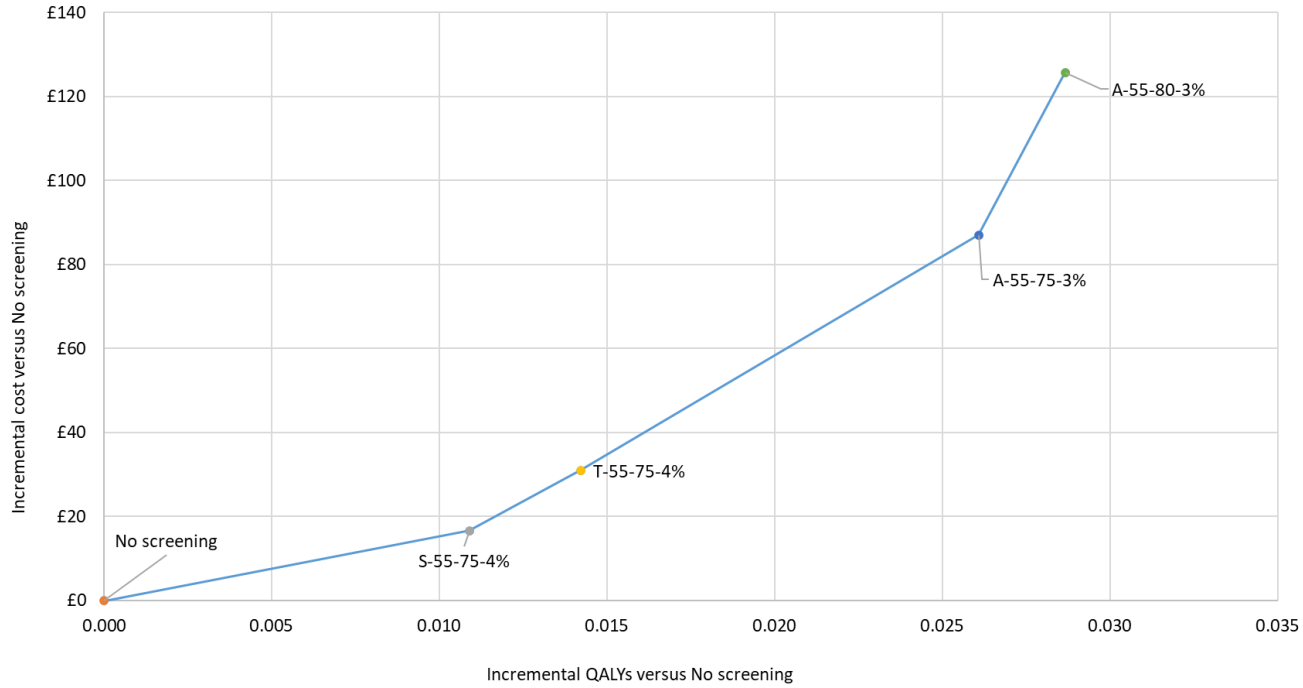


Table 18 Clinical outcomes for programme joiners by strategy on the cost-effectiveness frontier

	Strategy			
Secondary outcome	S-55-75-4%	T-55-75-4%	A-55-75-3%	A-55-80-3%
Mean number of screens per joiner	1.00	2.70	9.24	8.15
Proportion of diagnoses detected by screening (%)	48.1%	69.0%	86.5%	85.6%
Mean number of false positives per joiner	0.00	0.17	0.35	0.38
Mean lead time (months)	4.07	6.71	8.63	7.89
5-year lung cancer survival (%)	26.8%	38.1	46.3	41.9
Compared to No screening				
Change in lung cancer mortality (%)	-3.1	-4.1	-5.3	-4.7
Additional survival time with lung cancer (years)	3.50	4.97	6.11	5.46
Change in age at lung cancer diagnosis(years)	-1.66	-2.54	-3.24	-2.89
Change in age at death from lung cancer(years)	1.84	2.42	2.86	2.53
Change in age at death from other causes (years)	0.15	0.21	0.35	0.27
Per 100,000 programme joiners				
Number of screen-detected cases	1300	1933	4067	4967
Number of interval cancers	0	33	133	133
Additional lung cancer diagnoses (compared to no screening)	233	333	967	1300
Lung cancer deaths averted	433	567	1267	1400

Lung cancer mortality reduction

The average number of lung cancer deaths per 100,000 joiners of those screening strategies on the cost-effectiveness frontier was 18,686, compared to an average of 15,702 in the equivalent no screening populations. These strategies offer a benefit of approximately 3,000 fewer deaths due to lung cancer per 100,000 programme joiners. The lowest rate of lung cancer mortality across the screening strategies was 8.78%, A-60-75-3%; compared to 14.06% in the same population but without screening. The highest improvement in mortality is in the A-55-75-3% strategy (5.28%). The mortality estimates of strategies on the cost-effectiveness frontier are presented in

Table **19** for 100,000 joiners of each strategy.

Table 19 Lung cancer mortality in strategies on the cost-effectiveness frontier, per 100,000 joining participants

Strategy	Lung cancer mortality with screening	Lung cancer mortality without screening	Reduction in mortality	Risk ratio
S-55-75-4%	13.7%	16.8%	3.1%	0.969
T-55-75-4%	12.7%	16.8%	4.1%	0.959
A-55-75-3%	9.2%	14.4%	5.3%	0.947
A-55-80-3%	9.3%	14.0%	4.7%	0.953

Lung cancer stage and survival

Screening strategies were associated with an increased probability of lung cancer being diagnosed in the early stages (I and II) versus later stages (III and IV). Table 20 presents the stage distribution of diagnoses, regardless of whether these are diagnosed from clinical presentation or are screen-detected. Table 21 presents the stage distribution of screen-detected lung cancers only (thus there are no screen-detected cancers in the no screening strategy). In both tables, the average is taken across the populations of each programme design. The average ORs of early diagnosis for screen-detected cancers (geometric mean) were predicted to be 5.71, 5.70, 9.90 and 7.58 for single, triple, annual and biennial screening programmes, respectively.

Table 20 Stage distributions of diagnoses by presentation or LDCT screening

	Lung cancer stage						
Screening design	**Ia**	**Ib**	**IIa**	**IIb**	**IIIa**	**IIIb**	**IV**
No screening	5%	0%	0%	0%	1%	0%	93%
Single	14%	1%	0%	0%	8%	1%	75%
Triple	18%	1%	0%	0%	9%	1%	70%
Annual	30%	2%	1%	0%	9%	1%	57%
Biennial	22%	3%	1%	1%	9%	1%	62%

Table 21 Stage distributions of diagnoses as detected by LDCT screening only

	Lung cancer stage						
Screening design	**Ia**	**Ib**	**IIa**	**IIb**	**IIIa**	**IIIb**	**IV**
No screening	0%	0%	0%	0%	0%	0%	0%
Single	20%	3%	0%	1%	17%	2%	57%
Triple	21%	2%	0%	1%	13%	2%	62%
Annual	31%	2%	1%	0%	10%	1%	54%
Biennial	23%	4%	1%	2%	11%	2%	58%

Lung cancer diagnoses

Lung cancer screening led to increased lung cancer diagnoses across the lifetime of participants (i.e., what would be considered over-diagnosis) versus No screening. The number of lung cancer diagnoses per 100,000 participants was 18,154, 18,826, 18,258 and 19,507 for respective strategies on the cost-effectiveness frontier, S-55-75-4%, T-55-75-4%, A-55-75-3%, and A-55-80-3% (Table 22). The respective proportion of lung cancer diagnoses arising from screen-detection was 48.1%, 69.0%, 86.5% and 85.6%. Compared to no screening the overall relative risk of detection of lung cancer for the frontier strategies is 1.09, 1.14, 1.26 and 1.29, respectively.

Table 22 Lung cancer diagnoses in the strategies on the cost-effectiveness frontier, per 100,000 programme joiners

Strategy	Lung cancer diagnoses with screening	Lung cancer diagnoses without screening	Additional diagnoses	Relative risk of diagnosis
S-55-75-4%	18,154	16,585	1,569	1.095
T-55-75-4%	18,826	16,585	2,241	1.135
A-55-75-3%	18,258	14,503	3,755	1.259
A-55-80-3%	19,507	15,135	4,372	1.289

Number of screening tests and false positives

Screening programmes were associated with an average of 1.00 (100% compliance assumed), 2.69, 7.85, and 4.49 LDCTs per participant screened for single, triple, annual and biennial programmes respectively. The average number of false positives were 0.05, 0.20, 0.40, and 0.24 respectively.

Average ages at events

The average age at diagnosis of lung cancer was lower in the screening arms (which would be expected unless there was significant overdiagnosis in older participants). The average ages at diagnosis were 74.5, 73.6, 73.0 and 73.3 years for single, triple, annual and biennial programmes, respectively, versus a comparable 76.1 years in the absence of screening.

The average age at death from lung cancer was higher in the screening arms. The average ages at death from lung cancer were 78.9, 79.5, 79.8 and 79.5 years for single, triple, annual and biennial programmes, respectively, versus a comparable average of 77.4 years for no screening.

The average age at death from other causes was not significantly affected (around 82 years) but was slightly higher in the screening arms. The only explanation for this in the model is that some lung cancer patients were dying from other causes in the screening arms, whereas they died from lung cancer in the no-screening arm, and that these patients were on average older at time of death than the people already dying from other causes.

Lead time is calculated in the model as the difference between the age at which an individual is diagnosed with lung cancer in the no-screening arm (or dies from other causes, whichever is earlier) and the age at which the individual is diagnosed with lung cancer in the screening arm. Lead time is therefore time spent by the individual with a known diagnosis of lung cancer that they would not have had in the absence of screening. The average lead time in the single-screening arms was 0.34 years, whereas it was 0.57 years in the triple screening arms. The average lead time in annual screening arms was 0.75 years, whereas it was 0.67 years in the biennial screening arms.

Costs

The costs per participant relating to LDCT screening ranged from £107 (single-screen programmes) to £738 (annual screening programmes). Lung cancer costs (diagnosis, treatment and follow-up) also generally rose in line with the frequency of screening. If there are savings in the cost of treating some screen-detected cancers because they were detected at an earlier stage, these are outweighed by the increased number of lung cancers diagnosed (i.e., overdiagnosis). The costs of end-of-life care are decreased as the frequency of screening increases, because there is a reduction in the number of people dying of lung cancer (the model assumes end-of-life costs only for individuals dying of lung cancer, not for those dying of other causes with lung cancer).
The costs for the screening programmes on the cost-effectiveness frontier are shown in Table 23. The programmes are predicted to lead to population lifetime cost increases of £306M to £2,310M for a relevant population of 13 million ever-smokers aged 55–80 years.

Table 23 Costs for strategies on the cost-effectiveness frontier

	Strategy			
Cost item	S-55-75-4%	T-55-75-4%	A-55-75-3%	A-55-80-3%
Per Ever-smoker aged 55-80 years				
Screening programme admin	£5	£5	£5	£5
Total lifetime cost Without Screening	£3,479	£3,494	£3,550	£3,588
Per Programme joiner (lifetime)				
LDCT screens	£107	£252	£738	£659
Lung cancer intervention (diagnosis)	£4,510	£4,584	£3,828	£4,043
Lung cancer intervention (recurrence)	£87	£87	£67	£54
Lung cancer intervention (follow-up)	£416	£479	£471	£472
End of life	£520	£482	£359	£373
TOTAL	£5,641	£5,884	£5,463	£5,600
Ever-smoker pop., aged 55-80, 13m				
Screening administration (£,m)	£61	£61	£61	£66
LDCT screens (£,m)	£82	£193	£977	£1,081
TOTAL (£,m)	£45,230	£45,416	£46,144	£46,647
Additional cost vs No screening (£,m)	£217	£403	£1,131	£1,634

Deterministic sensitivity analysis

In the following deterministic analyses, results are reported in terms of incremental net monetary benefit (INMB) of S–55–75–4% (the optimal screening strategy in the base case analysis) compared to no screening at a willingness to pay (WTP) threshold of £20,000 per QALY.

The INMB is defined as:

> (incremental QALYs[of S-55-75-4% over no screening] multiplied by the WTP threshold) minus the incremental costs [of S-55-75-4% over no screening].

An INMB>£0 indicates that S-55-75-4% is cost-effective compared to no screening at a willingness to pay of £20,000 per QALY.

Univariate sensitivity analysis

In these univariate sensitivity analyses, each parameter, in turn, is increased and decreased by a fixed amount, 20%. This is not linked to the precision of that parameter, and no correlations between parameters are included.

Figure 6 Tornado diagram for univariate sensitivity analysis of S-55-75-4%. Parameters sorted by descending incremental NMB impact range; top 10 most impactful presented only.

There is some asymmetry in the tornado diagram (Figure 6) with the basecase result not falling within the bounds of some of the resulting ranges (i.e. including INMB of £0); this suggests at least some non-linearity in the model.

The results indicate some sensitivity in the parameters, with variation in seven of the parameters shown in Figure 6 leading to an INMB that would not be considered cost-effective at the £20,000 willingness to pay threshold. In other words, the reduction in INMB for the strategy S-55-75-4% is greater than £61. These parameters include increasing the incidence of lung cancer; decreasing the accuracy of predicting risk; and reducing baseline age.

Scenario analyses

A number of scenario analyses were conducted, in which changes to the structure or sets of parameter values were made. For each scenario analysis 3,000 individuals were simulated and the impact of the scenario analysis is assessed by presenting the INMB of S–55–75–4% versus no screening, as well as for up to two alternative screening strategies: (1) the strategy giving the highest INMB versus no screening of all screening strategies, and (2) the strategy on the cost-effectiveness frontier giving the highest INMB versus no screening of all screening strategies. The results of these scenario analyses are presented in Table 24.

Table 24 Results of Scenario Analysis

	INMB vs. No screening (£)			Alternative screening strategy	
Scenario	**S-55-75-4%**	**1**	**2**	**1: Highest INMB**	**2: Highest INMB on frontier**
Base case	£201				
Age distribution from smoking population	£170	£442	£442	A-55-80-3%	A-55-80-3%
Increased accuracy in prediction of risk	£286	£588	£588	A-55-80-3%	A-55-80-3%
Low programme uptake	£131	£292	£292	A-55-80-3%	A-55-80-3%
High programme uptake	£274	£610	£610	A-55-80-3%	A-55-80-3%
Tumour growth rate heterogeneity	£181	£261	£261	B-55-75-3%	B-55-75-3%
No survival gain for earlier diagnosis	£53	£53	£53	S-55-75-4%	S-55-75-4%
Half the survival gain for earlier diagnosis	£134	£238	£238	A-55-75-3%	A-55-75-3%
Increased HR-QoL disutility due to diagnosis anxiety	£201	£449	£449	A-55-80-3%	A-55-80-3%
Increased HR-QoL disutility due metastatic progression	£239	£586	£586	A-55-80-3%	A-55-80-3%
No screening anxiety after first screen	£201	£442	£442	A-55-80-3%	A-55-80-3%
No change in HR-QoL for false positive result	£201	£434	£434	A-55-80-3%	A-55-80-3%
PAS discount	£203	£457	£457	A-55-80-3%	A-55-80-3%
Social care costs excluded	£187	£429	£429	A-55-80-3%	A-55-80-3%
No end of life cost	£197	£430	£430	A-55-80-3%	A-55-80-3%
Lower unit cost of screening CT	£200	£434	£434	A-55-80-3%	A-55-80-3%
Higher unit cost of screening CT	£201	£437	£437	A-55-80-3%	A-55-80-3%
Time-horizon of only 10 years	£200	£455	£455	A-55-80-3%	A-55-80-3%
No discounting of future costs and QALYs	£66	£66	£66	S-55-75-4%	S-55-75-4%
No 3 month CT of indeterminate cases	£202	£457	£457	A-55-80-3%	A-55-80-3%
Steady state population	£36	£960	£960	B-55-80-3%	B-55-80-1%

HR-QoL, health-related quality of life; INMB, incremental net monetary benefit; QALYs, quality-adjusted life years

In summary, the scenario analysis results support the robustness of the outcome indicated by the univariate sensitivity analysis. Incremental net monetary benefit (at 3,000 simulations) remains positive in all cases for S-55-75-4%. The strategy delivering the highest net monetary gain over no screening (A-55-80-3%) is unchanged from the basecase in all but four scenarios. Introducing heterogeneity in the tumour growth rate brings the biennial programme to the fore; reducing the survival benefit of earlier diagnoses results in the displacement of annual screening by a single screen approach; similarly the removal of discounting of future costs and benefits; and the test of programmes in a steady-state population, where everyone enters programmes at near to minimum eligible age, promotes the biennial design (in the context of reduced risk thresholds of 1-3%).

Age distribution

This scenario involved a change from the UKLS age distribution of responders to the age distribution of smokers in the UK population. S-55-75-4% was replaced by S-60-75-5% (ICER £2,163 per QALY gained vs no screening) as the most cost-effective strategy on the frontier, with A-55-80-3% still the strategy of highest net-monetary benefit.

Risk-prediction accuracy

The accuracy of risk prediction was improved by changing the risk_lungcancer parameter in the risk model by an odds ratio of 1.5. In this scenario, S-55-75-4% was replaced by S-55-75-3% (ICER £484 per QALY gained vs no screening) as the most cost-effective strategy on the frontier. A-55-80-3% remained the strategy of highest net monetary benefit.

Programme uptake

When programme uptake was matched to the Manchester LHC recruitment programme, i.e., lower rate of response, higher uptake, and face to face risk assessment (higher cost), S-55-75-4% remained the most cost-effective strategy on the cost-effectiveness frontier (ICER £1,507 per QALY gained). Similarly, when a high participation is tested (response from 51% to 65%; join rate from 84% to 88%, S-55-75-4% remained the most cost-effective strategy on the cos-effectiveness frontier (ICER £1,492 per QALY gained). In neither alternative scenario did the strategies forming the cost-effectiveness frontier change, and in each case A-55-80-3% remained the strategy of highest net monetary benefit.

Incorporating heterogeneity in lung cancer progression

In this scenario analysis, the natural history model was recalibrated assuming heterogeneity between patients in the rate of lung cancer progression. This also affected the estimated sensitivity of LDCT screening (increasing it substantially). In this scenario, S–55–75–4% remained the most cost-effective strategy on the frontier (ICER £232 per QALY gained). The strategy of highest net monetary benefit changed from A-55-80-3% to T-55-75-3%.

Impact of mortality

In one scenario analysis, the survival benefit from early detection was eliminated (i.e., the survival is extended only by the lead time because of screening). In a second analysis, the survival benefit from early detection was halved. In each case, S–55–75–4% remained the most cost-effective strategy on the frontier (ICERs £6,237 and £2,808 per QALY gained, respectively). Without the benefit of earlier detection, S-55-75-4% dominated all other strategies; with half benefit, A-55-75-3% and A-55-80-3% moved to the frontier and offer higher net monetary gain.

Impact on health-related quality of life

In the first of these scenario analyses, it was assumed that there would be a short period of disutility following a lung cancer diagnosis, representing the impact on wellbeing of such a diagnosis. In the second, a larger disutility was assumed for stage IV lung cancer. In the third, it was assumed that there would be an impact on HRQoL in the run-up to every screen. In the fourth a disutility was applied for a period following a false positive result. In all four scenarios, there was no change to the most cost-effective strategy S-55-75-4%. Only the increased impact on utility of stage IV disease appreciably changed the ICER (£1,301 per QALY gained). The same four strategies formed the cost-effectiveness frontier in each scenario.

Commercial discounting of higher cost drugs

In this scenario of the estimated confidential commercial discount of high cost lung cancer drugs was increased from 50% to 70%. The cost-effectiveness frontier was not changed, with net monetary benefit over no screening only marginal improved (S-55-75-4%, ICER £1,393 per QALY gained).

Social care and End-of-life costs

When costs relating to social care were excluded (approximately one-third of lung cancer end-of-life costs) the cost-effectiveness frontier was unchanged and net monetary benefit over no screening was marginal reduced. The same pattern of low impact was observed when all end-of-life costs for lung cancer deaths were excluded.

Computed tomography screening costs

In the first of these scenario analyses, the cost of a LDCT scan was taken from the ‘Other’ setting descriptor for NHS trusts (£94.47 per CT), compared to £77.31 in the base case, the weighted cost across all NHS settings. In the second of these scenario analyses, the cost of a LDCT scan was taken from the ‘Outpatient’’ setting descriptor, representing a lower unit cost (£72.47 per CT). The cost-effectiveness frontier was not sensitive to either change with

respect to the dominant strategies; and the net monetary benefit over no screening was not sensitive even for those strategies with multiple screens.

Time horizon

The cost-effectiveness frontier was not sensitive to a time horizon reduced to 10 years from a lifetime (typically 15 life-years).

Discount rates

The removal of the annual discounting of future costs and benefits (3.5% in the base case) increases costs and QALYs with a destabilising impact on the ratio between the two. S-55-75-4% remains on the cost-effectiveness frontier and is the most cost-effective strategy (ICER £16,069 per QALY gained), and is joined by the only other strategy with a net monetary benefit versus no screening, S-55-75-3% (ICER £19,025 per QALY gained). Triple and annual strategies form the frontier with negative incremental benefit versus no screening.

Indeterminate cases

In this new scenario, we exclude cautionary CTs performed in these cases at three months (those at CTs at 12 months are retained even if not already scheduled via the programme). The overall impact is very slight, with no change to strategies forming the cost-effectiveness frontier and only very marginal increases in net monetary benefit versus no screening.

Population dynamics

This new scenario explores the impact of entry age distribution skewing heavily left towards minimum entry age in the range, as the screening eligible population mean age reduces as years pass since inception of the programme The 60-80 year range was tested only; entry age 61. This approximates a steady-state model. The initial result found that too few individuals met the minimum risk thresholds at 3%, 4% and 5% given the younger age range at entry, therefore risk thresholds were reduced to 1%, 2% and 3%. In this scenario, the S-55-80-1%, T-55-80-1%, and B-55-80-1% all dominated no screening. B-55-80-1% had the highest net monetary gain (£960).

Probabilistic sensitivity analysis

A PSA was conducted with 500 separate samples of parameter values and cohorts of 3,000 individuals sampled for each set of parameter values for a total of 1.5 million simulations. With cohort sizes of 3,000, it is likely that stability was not reached for strategy mean costs and QALYs for each parameter value, and that Monte Carlo variability affects the apparent variability in the PSA results. Nevertheless, there should be adequate exploration of the

parameter space with 500 samples and, with a total of 1.5 million simulations, the mean total costs and QALYs should be estimated with good precision.

Deterministic and probabilistic results were compared. As shown in Figure 7, there was good agreement between deterministic and probabilistic costs. The spread of probabilistic costs is relatively compressed, which is expected as a large proportion of the costs relate to screening and are less affected by outcomes for individuals.

Figure 8 shows that there was also good agreement between deterministic and probabilistic QALYs, again some compression. Figure 9 combines the cost and QALY variables using incremental net monetary benefit versus no screening. This shows a high correlation between analyses, although incremental net monetary benefit is slightly lower in the probabilistic analysis as might be expected given decreased range in strategy cost and QALYs (increments become compressed). However, given the very small incremental gains across strategies, those forming the cost-effectiveness frontier in the probabilistic analysis varied from the deterministic set of four (Table 25). The probabilistic cost-effectiveness frontier was formed by six strategies, with those single screen alternatives the most-cost-effective and the annual screen alternatives giving the highest incremental clinical and monetary benefit. As observed in the deterministic analysis, the probabilistic frontier strategies are all expected to be highly cost-effective at thresholds below £20,000 per QALY gained.

Figure 7 Comparison of deterministic and probabilistic costs

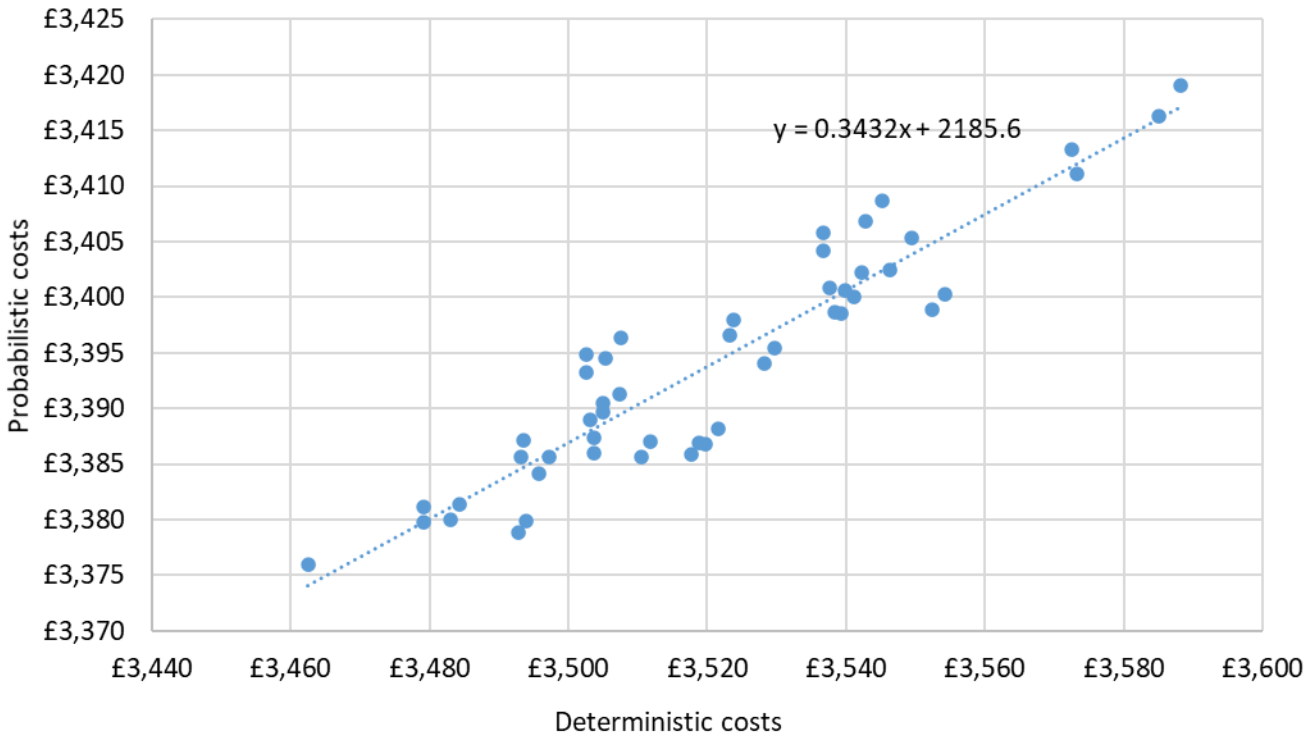


Figure 8 Comparison of deterministic and probabilistic QALYs

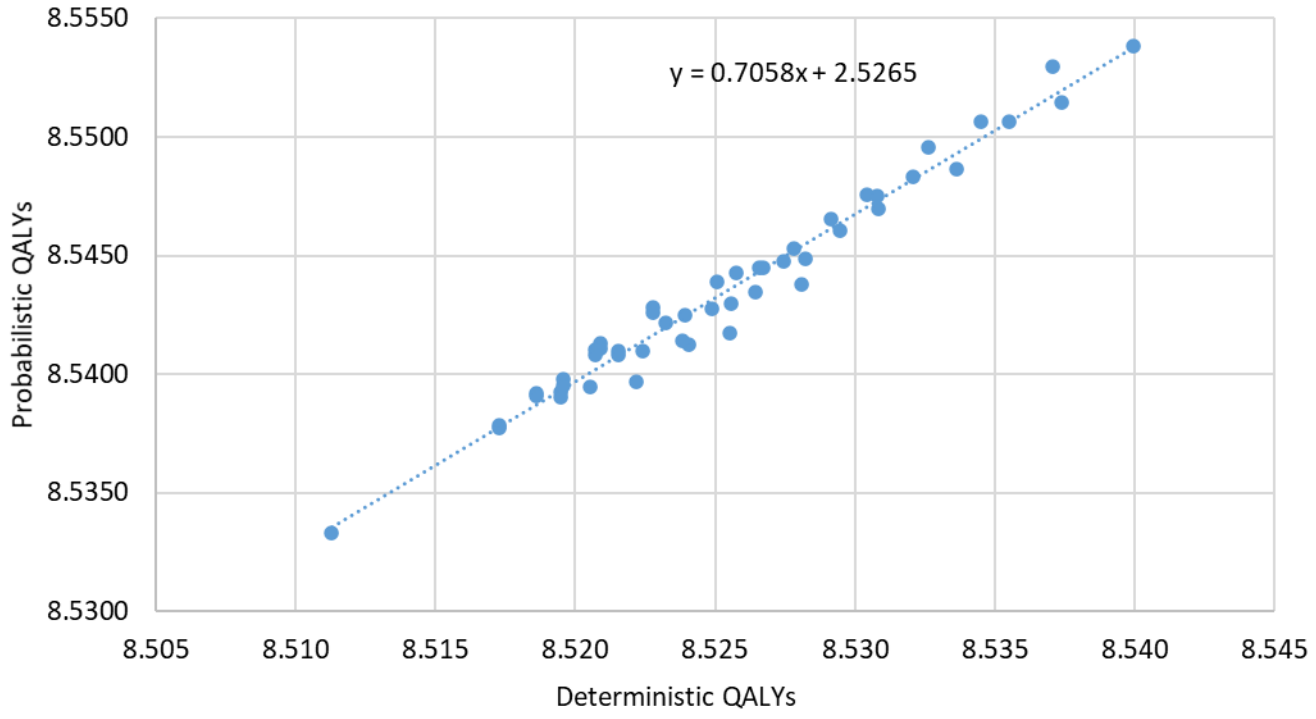


Figure 9 Comparison of deterministic and probabilistic INMB

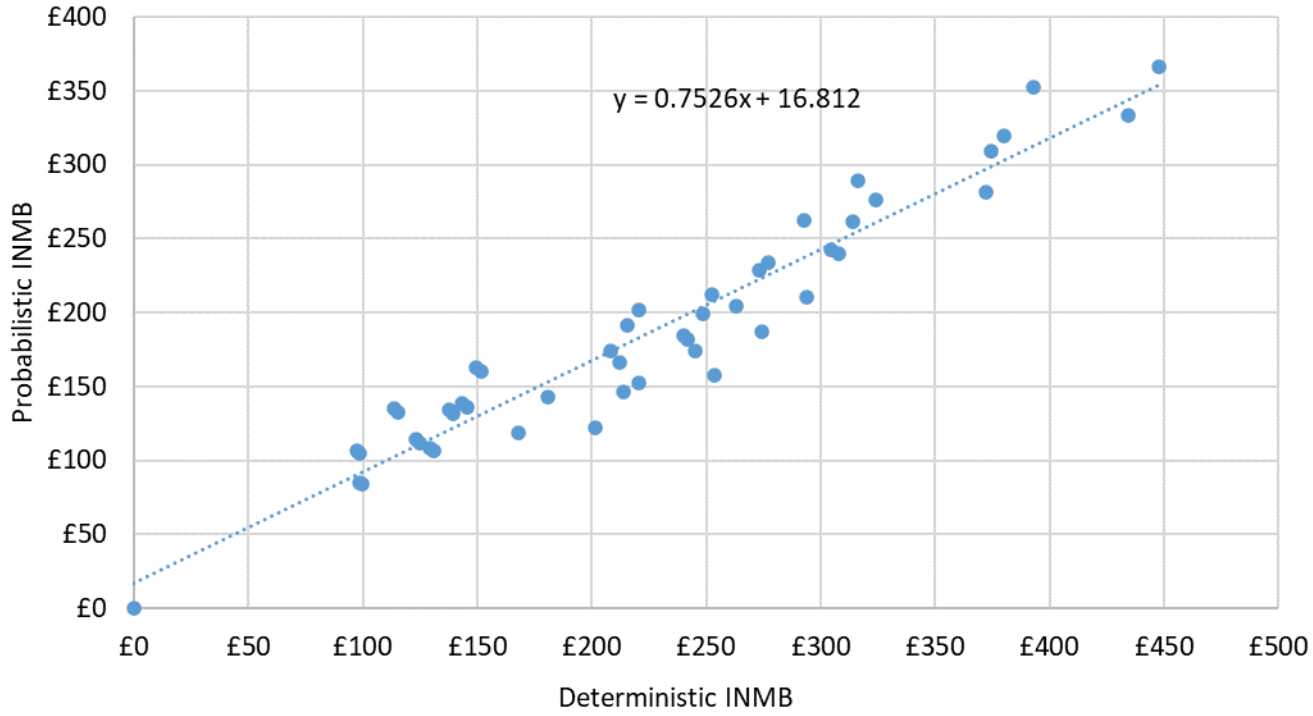


Table 25 Cost-effectiveness results from PSA

Strategy (ranked by ascending cost)	Costs (£)	QALYs	ICER vs No screening (£)	Full ICER (£)
No screening	£3,376	8.513	-	-
S-60-75-3%	£3,379	8.542	£101 (Dominant to £14,433)	£101
S-55-75-3%	£3,380	8.543	£136 (Dominant to £13,840)	£1,925
T-55-75-3%	£3,388	8.546	£377 (Dominant to £12,968)	£2,490
A-60-75-3%	£3,403	8.551	£715 (Dominant to £11,065)	£3,129
A-55-75-3%	£3,405	8.551	£773 (Dominant to £10,173)	£3,403
A-55-80-3%	£3,419	8.554	£1,071 (Dominant to £11,007)	£5,883

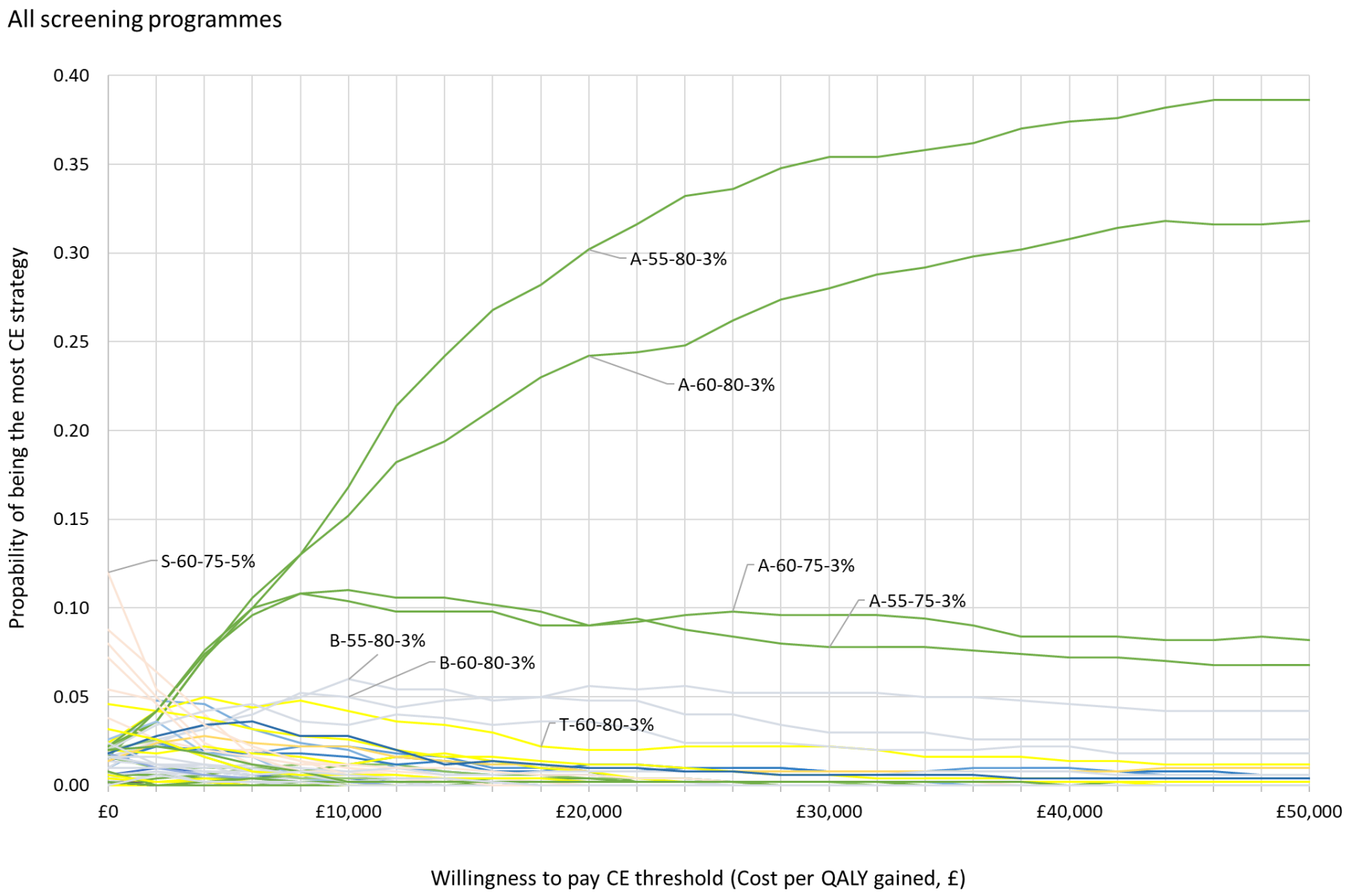
The probabilistic analysis suggests that a variety of lung cancer screening programmes are cost-effective at the £20,000 per QALY willingness to pay threshold. S-60-75-3% is the most cost-effective strategy (*c.f.* S-65-75-4%) in the deterministic analysis; and A-55-80-3%, the most comprehensive of all tested programmes, offers the highest net monetary gain (£367) versus no screening (whilst being cost-effective). Credible intervals at the 95% alpha level indicate that all the strategies forming the cost-effectiveness frontier are cost-effective, potentially dominating no screening (i.e., both less costly and more beneficial).

Figure 10 is an illustration of the set of PSA Monte Carlo simulations for each of the screening strategies on the ‘deterministic’ cost-effectiveness frontier. Also plotted are the means for both the ‘deterministic’ and probabilistic analyses. The spread indicates large variation in each direction relative to the spread of the means. The probabilistic means show a trend of smaller incremental cost and QALY differences relative to the deterministic result, but the sequence and shape of the two patterns are similar. The majority of simulations in all strategies fall below the £20,000 willingness to pay threshold, and many of these produce a dominant outcome where screening programmes are estimated to produce more QALYs at a lower cost than No screening.

Figure 11 presents the cost-effectiveness acceptability curves of tested populations and designs. Here we can observe the relative likelihood of each strategy being the single most cost-effective option across a range of willingness to pay thresholds. The two annual screening designs A-55-80-3% and A-60-80-3% are in fact the most likely to be optimally cost-effective at £20,000, with probabilities of 0.30 and 0.24, respectively. The probability of frontier strategy A-60-75-3% being the most cost-effective at this threshold is 0.09, equal to A-55-75-3%. Single screening strategies are predicted to be the most cost-effective at very low payer willingness but are not as good value as annual screening strategies at typical thresholds.

Figure 10 PSA simulations of frontier strategies on the cost-effectiveness plane

Figure 11 Cost effectiveness acceptability curve, all strategies



Discussion

Main findings

Updates to parameter values and limited revisions to the structure of the DES model have lead to 4 LDCT screening strategies lying on the cost-effectiveness frontier in base case analyses. Screening strategies were estimated to be more effective than no screening, suggesting a QALY gain of 0.006 to 0.0029 per person, depending on the strategy. Although such gains would not generally be considered significant, these gains are concentrated in people who join the screening programme (ranging from 3.6% to 12.6% of the population), are diagnosed with lung cancer at an earlier stage and, therefore, receive more substantial health benefits. However, screening strategies were estimated to be more costly than no screening, with an additional £16 to £126 cost per person. The results from this interim update suggest that LDCT screening would be cost-effective compared to no screening at a willingness to pay of £20,000 per QALY gained.

For the strategies on the cost-effectiveness frontier, the model estimated that LDCT screening reduced lung cancer mortality by 3.1% to 5.3% compared to no screening.

There is a pattern of increasing cost and QALYs as the number of screens in the programme design increases. The same pattern is observed in respect to lung cancer risk: lowering the threshold leads to increasing costs and QALYs.

For the strategy that was most cost-effective in the base case analyses, S-55-75-4%, deterministic sensitivity analyses demonstrated that these findings were robust to many changes in parameter values. As expected, increasing the uptake of LDCT screening, and the accuracy of the lung cancer prediction model (LLPv2), lead to higher INMB being estimated for LDCT screening compared to no screening. Decreasing the age of individuals at baseline lead to LDCT screening having a negative INMB.

Comparison with other model-based evaluations

UK-based evaluations

The interim report suggests that LDCT screening is likely to be a cost-effective use of NHS resources. This shift in estimated cost-effectiveness from the original ENaBL model(1)), which showed cost-effectiveness to be at the margins of what would be considered cost-effective in the NHS based on thresholds used by organisations like NICE, is to be expected given that many of the parameter revisions lead to values that were more

favourable to the screening strategies than the no screening strategy. For example, in the updated database search for relevant disutilities, we found evidence specifically on the utility, as measured by EQ-5D, of LDCT screening. Previously, assumptions were informed either by utility associated with chest x-ray screening, or using non-preference based measures of quality of life. Estimates of LDCT screening uptake are higher in the interim report compared to assumptions in the original report. These updated estimates are based on a regional screening trial (YLST), where the pathway to screening is more akin to what might happen in a national screening programme, than that assumed in the original model. Further evidence, based on updated nodule management guidance, has lead to a reduction in the proportion of indeterminate findings from LDCT screening, and the associated costs of further investigation.

A recently published review(2) identified 35 cost-effectiveness analyses of LDCT screening for lung cancer published since 2000. LDCT screening was generally found to be more effective and more costly than no screening. Reported ICERs ranged from US$1464 to US$2 million per QALY gained depending on policy question, setting, modeling approach, and evidence used (see Table 26). Four CEAs based in the UK were identified – Whynes(3), Field(4), Hinde(5) and the original EnABL report by Snowsill(1). All evaluated a single LDCT screen versus no screen. ICERs ranged from £8466 per QALY gained(4) to £28,169-£30,821 per QALY gained(1) depending on the eligible population. The results from this interim update analysis of ENaBL produce the most favourable cost-effectiveness estimates for a single LDCT screen in the UK, with an ICER of £1,529 per QALY gained (S-55-75-4).

Snowsill also evaluated annual screens for 3 years (referred to as triple screen), and annual and biennial screens for given age ranges. For the triple screen only one strategy was on the efficient frontier (T-55-80-3) ICER (vs no screening): £40,034/QALY(1). None of the annual and biennial strategies, were estimated to be on the efficient frontier. Again, the interim update analysis produces ICERs more favourable to LDCT screening ranging from £1,529 per QALY (for 3 annual screens) to £4,385 per QALY (for annual screens between 55 and 80 years old), with no biennial screening strategies on the cost-effectiveness frontier. Note that ENaBL is the only UK-based model that has evaluated annual and biennial LDCT screening strategies. However, the closeness of many strategies to the cost-effectiveness frontier, means that this interim model should not be used to base conclusions about the relative cost-effectiveness of one strategy to another.

Peters(2) reported on the variability of modelling approach, and concluded that those models incorporating a natural history component for lung cancer were more likely to adequately address critical appraisal items, but stressed that these are difficult to validate appropriately. The modelling approach taken by Whynes(3), Field(4) and Hinde(5) are

similar, essentially using a decision tree approach where the effectiveness of LDCT screening is represented by an explicit stage shift at diagnosis – with those diagnosed via screening assumed to be diagnosed at an earlier stage. Consideration of overdiagnosis in these analyses is unclear, pre-determined estimates of lead-time are assumed and few sensitivity analyses are reported. Although the data informing Whynes(3) is hypothetical, due to a lack of trial data at that time, the data used in Field(4) and Hinde(5) are from the UK. As discussed in the Background to this interim report, Snowsill(1) use a DES model incorporating a natural history model. This approach has advantages of implicitly considering issues such as lead-time bias and overdiagnosis, and is calibrated on data from the largest lung cancer screening trial conducted so far (NLST). However, the calibration of stage distributions at diagnosis in ENaBL is not as expected compared to the NLST and other trial data (hence the continuing work to update the natural history model). It is worth noting that the ENaBL model has received intense scrutiny as a result of the Modelling Task and Finish Group meetings organised through the NSC. Whilst welcoming this, it is possible that if equivalent scrutiny had been directed at other UK-based evaluations, then these too would have required further development to provide more valid estimates of cost-effectiveness.

International evaluations using the CISNET models

Among the other published CEAs, Peters identified a number of studies using models with a natural history component. Consideration of these models may provide context for the ENaBL model. Four of these are part of the US National Institute for Health Cancer Intervention and Surveillance Modeling Consortium and as such are registered with the Cancer Intervention and Surveillance Modeling Network (CISNET). They are MISCAN-Lung, lung cancer policy model (LCPM), lung cancer outcomes simulator (LCOS) and the model from the University of Michigan, see Table 26.

The MISCAN-Lung model has been used to evaluate LDCT screening versus no screening in Canada(41) and Switzerland(45). In Canada, annual screening strategies were associated with ICERs of Can$39,000/LY to Can$64,500/LY (cost year 2015) depending on age and smoking history of eligible population(41). In Switzerland, evaluation of annual screening strategies lead to ICERs of €30,500/LY to €48,500/LY depending on age and smoking history of eligible population were estimated(45). Comparison with ENaBL is difficult as analyses per QALY gained were not reported. However, ICERs per QALY gained would be greater than those reported per LY gained. It is worth noting that, although not stated explicitly, the WTP per QALY gained in Canada is generally thought to be around Can$50,000.

The LCPM was used in McMahon(46) to evaluate single and annual screening vs no screening in the US with a cost-year of 2006. Depending on gender, age group and smoking history of eligible population, ICERs (compared to no screening) ranged from US$144,000 - $207,000/QALY for single LDCT screens and $110,000/QALY - $203,000/QALY for annual screening. Criss(47) recently evaluated annual screening in the US starting at age 55 years old, with different upper age limits using all four of these CISNET models (cost year 2018). They reported average ICERs across the 4 models of $49,200/QALY (stopping at age 74), $68,600/QALY (stopping at age 77), $96,700/QALY (stopping at age 80), see Table 26. As with Canada, it is generally thought that the WTP per QALY gained in the US is around US$50,000. However, the USPSTF does not consider cost-effectiveness in their decision-making.

As noted in Peters(2), making comparison between different evaluations of cost-effectiveness is not straightforward, due to the multiple sources of heterogeneity. However, simple, naïve, comparison of ICERs between McMahon and Criss suggest that LDCT is seemingly more cost-effective in the US now than it was 15 years ago.

The UK-based studies report lower ICERs than those based on the CISNET models. There are many differences between the analyses, including the modelling approach and the strategies evaluated. With the exception of Snowsill(1), the UK-based studies use decision tree approaches, while the CISNET models use more complex models incorporating the natural history of lung cancer. The UK-based studies have focussed on single screening, while the CISNET models have focussed more on the cost-effectiveness of annual screening. McMahon(46) and Snowsill being the exceptions. The original ENaBL model assessed both, finding that a single screen was generally more cost-effective than annual screening.

As this summary of UK-based and CISNET models suggest, analyses based on more complex natural history-based models have tended to produce higher ICERs than those using decision tree approaches. Peters(2) also found that they tended to address more of the challenges of evaluating cancer screening programmes than less complex models.

The interim updated ENaBL results indicate that LDCT screening could be cost-effective compared to no screening, in line with earlier published analyses set in the UK. However, limitations of all of these studies, including ENaBL, have been noted. The ICERs estimated in the interim updated ENaBL model are much more favourable to screening strategies than those reported in Snowsill(1) or in the CISNET model-based analyses. These are emerging findings which are significant and worthy of attention given the contrast with the results reported by Snowsill in 2018. However, a more conclusive statement of the cost-

effectiveness of LDCT in the UK requires the ongoing work to address the criticisms of the natural history component of ENaBL to be completed and incorporated into the model.

Having a UK-based model, that adequately addresses the challenges of evaluating lung cancer screening programmes, will provide the most appropriate estimates of cost-effectiveness for the UK. The findings within this interim report take us a step closer, but the main limitations of ENaBL remain. The final report, incorporating the new natural history component, should clarify uncertainties as to the impact on results from addressing the criticisms.

Table 26 Characteristics and results of UK-based models and CISNET registered models by screening frequency

Model	Country	Cost-year	Eligible population	Incremental costs (vs no screening) per person	Incremental effects (vs no screening) per person	ICERs (vs no screening)
Single screen						
Interim ENaBL	UK	2020	55-75 years, ≥4%	£17	QALYs: 0.011	£1,529 per QALY
Original ENaBL(1)	UK	2016	Aged 60-75 years, ≥3%	£23	QALYs: 0.0008	£28,169 per QALY
			Aged 55-75 years, ≥3%	£3	QALYs: 0.0001	£28,784 per QALY
			Aged 55-80 years, ≥3%	£6	QALYs: 0.0001	£30,821 per QALY
Whynes(3)	UK	2004	Men aged 61 years at high risk	£201	QALYs: 0.01	£14,000 per QALY
Field(4)	UK	2016	Adults aged 50–75 years, at =>5% risk of lung cancer	£565,498	QALYs: 66.8	£8466 per QALY
Hinde(5)	Manchester	2015	55-74yrs ever smokers with 6-year lung cancer risk of ≥1.51%	£40	QALYs: 0.004	£10,069 per QALY

LCPM McMahon(46)	US	2006	Aged 50-70, 60-74, 70-74 with current & former =>20 pack-year history	US$1,778 to US$3,637	QALYs: 0.009 to 0.022	US$144,000 to $207,000/QALY
Annual screening (for 3 years)						
Interim ENaBL	UK	2020	Aged 55-75 years, ≥4%	£31	QALYs: 0.015	£2,179 per QALY
Original ENaBL(1)	UK	2016	Aged 55-80 years, ≥3%	£17	QALYs: 0.0002	£40,034 per QALY
Annual screening (for age group)						
Interim ENaBL	UK	2020	Aged 55-75 years, ≥3%	£87	QALYs: 0.026	£3,336 per QALY
Interim ENaBL	UK	2020	Aged 55-80 years, ≥3%	£125	QALYs: 0.029	£4,385 per QALY
Original ENaBL(1)	UK	2016	Various			None on the efficient frontier
MISCAN(41)	Canada	2015	10-40 pack-years. 10 - 20 years since smoking cessation.	Can$498 to $2067	LYs: 0.013 to 0.032	Can$39,000 to $64,500 per LY
MISCAN(45)	Switzerland	2015	10-40 pack-years. 10-20 years since smoking cessation.	€641 to €1885	LYs: 0.021 to 0.039	€30,500 to €48,500 per LY
LCPM McMahon(46)	US	2006	Aged 50-70, 60-74, 70-74 with current & former =>20 pack-year history	NR	NR	$110,000/QALY $203,000/QALY depending on gender, age group and smoking history of eligible population.

LCOS Toumazis(48)	US	2019	20-40 pack-years.10-20 years smoking cessation	US$903 to $2,391	QALYs: 0.0161 to 0.0193	US$55,968/QALY to US$124,147/QALY depending on age and smoking history of eligible population and whether disutility for indeterminate results included
Criss(47)	US	2018	Lower age limit 55 years.	US$870 to $980	QALYs: 0.019 to 0.021	Average across the 4 models: $49,200/QALY (stop at age 74), $68,600/QALY (stop at age 77), $96,700/QALY (stop at age 80)
Biennial screening						
Interim ENaBL	UK		Various			None on the efficient frontier
Original ENaBL(1)	UK	2016	Various			None on the efficient frontier
MISCAN(45)	Switzerland	2015	30-40 pack-years.	€324 to €6100	LYs: 0.013 to 0.020	€25,500 to €31,000 per LY
LCOS Toumazis(48)	US	2019	30-40 pack-years, 10-15 years smoking cessation.	US$282 to $1,033	QALYs: 0.0065 to 0.0134	US$43118/QALY – US$76909/QALY depending on age and smoking history of eligible population, and inclusion of disutility for indeterminate results
MISCAN(41)	Canada	2015	Various			None on the efficient frontier
Triennial screening						
MISCAN(45)	Switzerland	2015	30-40 pack-years.	€333	LYs: 0.012	€27,374 per LY

LCOS, Lung Cancer Outcomes Simulator; LCPM, Lung Cancer Policy Model; LY, life-year; QALY, quality-adjusted life-year

Strengths

The model was developed by an independent research group, and has been scrutinised and updated in response to detailed probing by clinical and health economic modelling experts. This will ultimately contribute towards the validity of the model. It will also be particularly important in the future if lung cancer screening is implemented to assist with any future assessment of modifications to a screening programme.
Although the interim report does not address all the challenges in the modelling of lung cancer screening, it has greatly improved the quality of the parameters through the collaboration and support of clinical experts in the field.

Limitations

The main limitation to the results presented in this interim report is that the natural history model component is completely unchanged from the original model. As Table 21 shows, the stage distributions at screen-detected lung cancers are still high for stage IV, and very low for earlier stages. The impact of this on estimates of cost-effective was discussed in early engagement meetings, with agreement that this would underestimate the effectiveness (and cost-effectiveness) of LDCT screening compared to no screening, since the value of screening is to identify cancers at earlier stages than they would present clinically. Thus, it might be assumed that when the updated natural history model is complete, the cost-effectiveness of LDCT will look even more favourable. However, there are other changes to the natural history model that were identified as important in early meetings (see

Table 1), and the impact of these may actually lead to less favourable cost-effectiveness estimates. For instance, incorporating heterogeneity in the progression of pre-clinical lung cancer should lead to better capture of overdiagnosis through screening and fast-growing cancers being more likely to be picked up between screening rounds rather than at screening.

The model does not consider the costs or health impacts of incidental findings from LDCT screening. Thus, any additional benefits unrelated to lung cancer that may arise from LDCT screening have not been incorporated.

The data source for disutilities associated with LDCT screening, used in the basecase analysis, only reports disutilities associated with positive LDCT results, and not false positive LDCT results. More detailed data on disutilities associated with LDCT screening would be desirable. As the database search for utilities was conducted 12 months ago, any studies reporting relevant utility data published in the last 12 months has not been considered for this interim report. The final report will include an update of the database searches.

Summary

Conclusions and implications for policy

Based on the results presented in this interim report, the use of LDCT for lung cancer screening is likely to be cost-effective compared to no screening. This change in estimates of cost-effectiveness from the original model(1) is driven by the use of updated parameters, which are based on more appropriate data and assumptions than in the original. Furthermore, these updated parameters are more likely to favour LDCT screening than no screening. However, the natural history model used is completely unchanged from that in the original model, which received warranted criticism on a number of counts. Therefore, the interpretation of cost-effectiveness results reported here need to be interpreted in the knowledge that there are many limitations still with the reported results. Nevertheless, given that the ICER for the most cost-effective strategy in this interim report is £1,529 per QALY gained, the updated natural history model component would need to lead to an order of magnitude change for the ICER to get close to the willingness to pay threshold of £20,000 per QALY, as used by organisations like NICE. A final report will be produced when the new natural history component has been completed.

Due to this update being part funded by the National Institute of Health Research (NIHR), we are prohibited from making policy implications.

Continuing development of ENaBL is important, not just to improve the performance of the natural history component, but also to provide a valid model with widespread acceptance which can be used to evaluate modifications to a lung cancer screening programme should it be introduced. This could include the impacts of smoking cessation and incidental findings. Such a model will also be useful to other groups assessing the cost-effectiveness of other approaches to reducing the morbidity and mortality of lung cancer (we have been approached by these groups asking permission to use the model when it is completed).

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