Variation in Model-Based Economic Evaluations of Low Dose Computed Tomography (LDCT) Screening for Lung Cancer: a Methodological Review

Jaime L. Peters[1]*, Tristan M. Snowsill[2], Edward Griffin[1], Sophie Robinson[3], Chris J. Hyde[1]

*Corresponding author, j.peters@exeter.ac.uk

[1]Exeter Test Group, University of Exeter Medical School, Exeter, England

[2]Health Economics Group, University of Exeter Medical School, Exeter, England.

[3]PenTAG , University of Exeter Medical School, Exeter, England.

Author Contributions: Concept and design: Peters, Snowsill, Robinson, Hyde

Acquisition of data: Peters, Robinson

Analysis and interpretation: Peters, Griffin, Hyde

Drafting of the manuscript: Peters, Snowsill, Griffin, Robinson

Critical revisions of paper for important intellectual content: Peters, Snowsill, Griffin, Hyde

Obtaining funding: Hyde

Conflict of interest disclosure:

The authors reported no conflicts of interest.

Funding support: This work was supported by the UK NIHR Health Technology Assessment Programme (14/151/07).

Role of Funder/Sponsor:

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgements: We thank Jenny Lowe who helped with additional document retrieval.

Abstract

Objectives: There is significant heterogeneity in the results of published model-based economic evaluations of low dose computed tomography (LDCT) screening for lung cancer. We sought to understand and demonstrate how these models differ.

Methods: An expansion and update of a previous systematic review (n=19). Databases (including Medline and Embase) were searched. Studies were included if strategies involving (single or multiple) LDCT screening were compared to no screening or other imaging modalities, in a population at risk of lung cancer. More detailed data extraction of studies from the previous review was conducted. Studies were critically appraised using the Consensus Health Economic Criteria list.

Results: Sixteen new studies met the inclusion criteria, giving a total of 35 studies. There are geographic and temporal differences, and differences in screening intervals and eligible populations. Studies varied in the types of models used, e.g. decision tree, Markov, microsimulation models. Most conducted a cost-effectiveness analyses (using life years gained) or cost-utility analysis. The potential for overdiagnosis was considered in many models, unlike with other potential consequences of screening. Some studies report considering lead-time bias, but fewer mention length bias. Generally, the more recent studies, involving more complex modelling, tended to meet more of the critical appraisal criteria, with notable exceptions.

Conclusions: There are many differences across the economic evaluations contributing to variation in estimates of the cost-effectiveness of LDCT screening for lung cancer. A number of methodological factors and evidence needs have been highlighted that will require consideration in future economic evaluations to achieve better agreement.

Highlights

What is already known about the topic?

- Evidence from RCTs indicates that screening is effective at reducing lung cancer deaths, the question of whether it is cost-effective remains uncertain.
- There are a large number of economic evaluations in the literature, and the findings from these vary.

What does the paper add to existing knowledge?

- This paper highlights the many methodological considerations made in model-based economic evaluations of LDCT screening for lung cancer and shows important differences between the published economic evaluations.

What insights does the paper provide for informing healthcare-related decision making?

- This paper provides a basis for deeper comparisons of economic evaluations of LDCT screening for lung cancer, highlighting the different methodological approaches.
- It informs future economic evaluations on the challenges of modelling, the type of approaches taken and the route to achieving greater agreement on the cost-effectiveness of LDCT screening.
- Policy-makers should be aware important choices are made when economic evaluations are conducted on their behalf, and should satisfy themselves that the choices are appropriate.

Introduction

Once symptomatic, lung cancer generally has poor prognosis, so there is great potential to identify individuals with asymptomatic lung cancer and commence treatment earlier in the hope of improving prognosis. Trials suggest that low dose computed tomography (LDCT) screening for lung cancer is effective at reducing lung cancer mortality[1] compared to no screening or other screening modalities. Evidence for associated reductions in all-cause mortality is less certain: NELSON[2] report a risk ratio (RR) of 1.01 (95% CI 0.92 to 1.11), while a meta-analysis[3] of MILD, DANTE, DLCST and NLST reported a RR of 1.00 (95% CI 0.87 to 1.16).

The cost-effectiveness evidence for LDCT screening for lung cancer is more variable. A review [3] identified 19 model-based economic evaluations of LDCT screening for lung cancer. They reported that although LDCT screening was generally found to be more effective than the comparator (in terms of quality-adjusted life-years (QALYs) and/or life-years (LYs) gained), it was more expensive. Incremental cost-effectiveness ratios (ICERs) ranged from US$1,464 per QALY gained[4] to >US$100,000 per QALY gained[5,6].

Variability in results may be expected given differences in policy questions, populations, and settings, among other aspects of study design. Variation in methodological approach was also identified, which is not surprising since decisions need to be made when conceptualizing and designing model-based economic evaluations[7]. These include which type of model to implement (e.g. decision tree, Markov, microsimulation), the model structure (e.g. states in a Markov models, stages in a natural history model), how effectiveness is captured, which outcomes and costs are accounted for, type of economic evaluation (cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA)), whether and how potential harms and/or biases are considered.

Radiation exposure is a potential harm with LDCT screening, and estimated effective radiation doses for one LDCT screen range from 0.65mSv to 2.36mSv[8]. But there is little data on patient related outcomes. Estimates of overdiagnosis of 0% to 67.5% associated with LDCT screening have been reported [8]. Overdiagnosis is where the target condition is detected by screening and treated, but would have never been clinically significant during the individual's lifetime.[8]. By not considering potential overdiagnosis in models all cancers identified in the screening arm are assumed to have led to clinical implications for the patient, and this may not be the case. Therefore, the cost-effectiveness of LDCT screening is likely to be overestimated (i.e. lowering the ICER) because costs and health losses associated with overdiagnosed cancers are inappropriately included in the no screening arm.

There is also the issue of incidental findings: where there is no evidence of cancer, but some other condition or concern that may require further examination is identified. The NLST reported that 10.2% of participants screened by LDCT had a negative result but potentially important noncancerous abnormality[9]. NELSON reported 8% of 1,929 participants had potentially important findings, 79% were subsequently found to be clinically relevant[10]. Dealing with incidental findings, regardless of whether further investigation leads to the identification of important clinical findings, involves additional costs and impacts on patients.

Lead-time bias and length bias also need to be considered in evaluations of screening programmes. Lead-time bias is the inflation of survival estimates in a screening study as an artefact of moving the date of diagnosis earlier without necessarily delaying the date of death. Length bias is the tendency of screening studies to identify slowly progressing malignancies but not rapidly progressing cancers. If length bias is not considered analyses are likely to overestimate the effectiveness of screening.

We were commissioned by the UK's National Institute for Health Research to update the evaluation of effectiveness and cost-effectiveness evidence on LDCT screening for lung cancer [3]. In summarising the cost-effectiveness evidence we sought to explore differences in the policy questions, general modelling methods and approaches to dealing with potential harms and/or biases. We present how different economic evaluations have dealt with these issues. Ideally, we would want to determine how the different approaches affect the resultant cost-effectiveness estimates. However, due to the multiplicity of modelling approaches and decisions, this is not something that can be realistically achieved in a review of published models. Instead, our aim is to highlight the importance of understanding that these models are different, that they differ in a multitude of ways, and these differences need to be clearly understood before interpreting and comparing the cost-effectiveness results.

Methods

This is an expansion and update of a systematic review of economic evaluations of LDCT screening for lung cancer [3] (PROSPERO registration CRD42016048530). The search strategies previously developed[3] were used for the update, including searching Medline, Embase, and EconLit (see Appendix 1 for databases searched and Medline search strategy). No changes were made to the original criteria (Appendix 2).

One reviewer (JP) screened titles/abstracts, and subsequent full-texts for inclusion. To fulfil our aim a more detailed data extraction of studies than that previously conducted[3] was required. The additional items were how the effectiveness of LDCT screening is modelled, whether all-cause mortality is adjusted for the high risk populations modelled, what lung cancer stages are modelled; and whether and how overdiagnosis, lead-time bias, length bias,

incidental findings (observations requiring further investigation/treatment that are not lung cancer) and radiation exposure from the LDCT scan were considered in the models, and any reporting of model validation. The CHEC (Consensus Health Economic Criteria) critical appraisal tool used previously[3] was applied to studies identified in the updated searches (see Appendix 6).

Results

1738 hits were identified. After deduplication and title/abstract screening, 49 full-texts were obtained. 15 studies met the inclusion criteria. Another study, identified from reference lists of included studies, was also included. Including the 19 studies previously identified[3], gives a total of 35 included studies (see Figure 1). The reported ICERs range from US$1,464 to US$2million per QALY gained depending on policy question, setting, modelling approach and evidence used. A summary of the base case cost-effectiveness results from each study is given in Appendix 3, but not discussed further.

Figure 1 here

We describe the different policy questions evaluated, the general modelling approaches used, whether and how the models considered overdiagnosis, incidental findings, lead-time and length bias, and radiation exposure from the LDCT scan. Reports of validation of the models are also summarised.

Policy questions

The policy questions evaluated are (see summary in Table 1 and Appendix 4):

- single (one-off) LDCT screens (n=8);
- annual LDCT screens varying by duration: 3, 5 or 20 years, or defined in terms of eligible age range (n=26). Nine studies evaluated annual LDCT screens for 3 years compared to no screening (n=6) or chest x-ray (n=2). Five studies evaluated annual LDCT screens for 5 years vs no screening. Thirteen evaluations compared annual LDCT screens over specified age ranges to no screening[3,5,6,11-20], and one to chest x-ray[21]
- biennial LDCT screens, defined by specific ages compared to no screening (n=7). One study compared the cost-effectiveness of biennial LDCT screening with annual LDCT screening.
- triennial LDCT screens (n=1).

For most studies the comparator is no screening. Many evaluations define the eligible population as that used in the NLST: individuals aged 55-74 years with ≥30 pack-year smoking history. The majority of studies report a healthcare payer's perspective, using a 3% discount rate for future costs and outcomes.

Table 1 Summary of policy questions and strengths and weaknesses of each model (sorted by year of publication)

Author, year	Country, Cost year	Analysis	Screening frequency	Main strengths of modelling approach	Main weaknesses of modelling approach*
Marshall et al 2001[22]	US, 1999	CEA	Single	Considers impact of lead time bias, appropriate	Not based on RCT data, 5 year time horizon, all-cause mortality not for

				resources, costs and outcomes	high-risk groups, no consideration of overdiagnosis
Marshall et al 2001[23]	US, 1999	CUA CEA	Annual (5 years)	Considers impact of lead time bias, appropriate resources and costs	Not based on RCT data, 5 year time horizon
Chirikos et al 2002[24]	US, 2000	CEA	Annual (5 years)	15 year time-horizon, appropriate resources and costs	Not based on RCT data, no consideration of overdiagnosis or lead/length bias
Wisnivesky et al 2003[25]	US, 2000	CEA	Single	Lifetime horizon, considers lead time bias	Not based on RCT data
Manser et al 2005[26]	Australia, 2002	CUA CEA	Annual (5 years)	15-year time horizon, CT accuracy based on published literature, considers overdiagnosis and lead-time bias	No consideration of length bias
Mahadevia et al 2003[5]	US, 2001	CUA	Annual (by age)	40 year time-horizon, considers overdiagnosis and lead/length bias	Not based on RCT data, hypothetical stage shift assumption

Whynes et al 2008[27]	UK, 2004	CUA	Single	Lifetime horizon, considers impact of lead-time bias	Not based on RCT data, no consideration of overdiagnosis
McMahon et al 2011[6]	US, 2006	CUA	Single Annual (by age)	Lifetime horizon, calibrated to RCT data, considers overdiagnosis and lead-, and length bias	Few sensitivity analyses
Goulart et al 2012[28]	US, 2011	CEA	Unclear	Use RCT data, considers overdiagnosis	1 year time horizon, no consideration of lead/length bias, limited outcomes (lung cancer deaths)
Pyenson et al 2012[13]	US, 2012	CEA	Annual (by age)	15 year time horizon, considers overdiagnosis and lead-time bias	Not based on RCT data, no discounting reported
Shmueli et al 2013[4]	Israel, 2012	CUA	Single	Lifetime horizon, considers overdiagnosis and lead-time bias	Based on data from single-centre cohort study in Israel
Villanti et al 2013[14]	US, 2012	CUA	Annual (by age)	15 year time horizon, use RCT data, considers lead-time bias	No discounting reported, no consideration of

					overdiagnosis, few sensitivity analyses
Black et al 2014[29]	US, 2009	CEA CUA	Annual (3 years)	Lifetime horizon, direct modelling of RCT data, considers overdiagnosis, considers costs of dealing with incidental findings and future cancers due to LDCT radiation exposure	No mention of lead- or length time bias, few sensitivity analyses
Pyenson et al 2014[12]	US, 2014	CEA	Annual (by age)	15 year time horizon, use RCT data, considers overdiagnosis (in sensitivity analysis) and lead-time bias	No discounting reported, few sensitivity analyses
Tabata et al 2014[21]	Japan, NR	CEA	Annual (by age)	Lifetime horizon, considers overdiagnosis	No discounting reported, based on Japanese case-control study
Goffin et al 2015[11]	Canada, 2008	CUA	Annual (3 years)	20-yr time horizon, calibrated to NLST, considers overdiagnosis, lead- and length-time bias	Few sensitivity analyses

Field et al 2016[30]	UK, 2016	CUA	Single	Lifetime horizon, considers lead-time bias	Based on pilot RCT data, few sensitivity analyses
Goffin et al 2016[31]	Canada, 2008	CUA	Annual (by age)	Lifetime horizon, calibrated to NLST, considers lead-time bias	No consideration of overdiagnosis, few sensitivity analyses
ten Haaf et al 2017[15]	Canada, 2015	CEA	Annual (by age) Biennial (by age)	Lifetime horizon, calibrated to RCT data, considers overdiagnosis, lead-time and length bias	Few sensitivity analyses
Cressman et al 2017[32]	Canada, 2015	CUA	Annual (3 years)	30 year time horizon, uses RCT data, considers overdiagnosis (in sensitivity analyses)	Unclear consideration of lead/length bias
Treskova et al 2017[33]	Germany, 2016	CEA	Annual (5 years)	Lifetime horizon, considers overdiagnosis, lead-time and length bias, validation against NLST	Evidence source unclear, few sensitivity analyses
Yang et al 2017[34]	Taiwan, 2013	CUA	Annual (3 years)	Lifetime horizon, uses RCT data, considers lead-time bias, validated	No consideration of overdiagnosis, few sensitivity analyses

				against observed data	
Hinde et al 2018[35]	UK, 2015	CUA	Single	Lifetime horizon, considers lead-time bias	Data on pilot data, no report of considering overdiagnosis, few sensitivity analyses
Kumar et al 2018[36]	US, 2016	CUA CEA	Annual (3 years)	Lifetime horizon, use RCT data, considers overdiagnosis, report calibration results	Unclear if considers lead-time bias, few sensitivity analyses
Tomonaga et al 2018[16]	Switzerland, 2015	CEA	Annual (by age) Biennial (by age)	Lifetime horizon, calibrated to RCT data, considers overdiagnosis	No mention of lead- or length-time bias, few sensitivity analyses
Wade et al 2018[37]	Australia, 2015	CEA CUA	Annual (3 years)	10 year time horizon, use RCT data, all-cause mort adjusted for smoking status	No consideration of overdiagnosis, lead/length bias
Snowsill et al 2018[3]	UK, 2016	CUA	Single Annual (3 years)	Lifetime horizon, calibrated to RCT data, considers overdiagnosis, lead- and length-time bias	Generalisability of findings not discussed, no external validation reported

			Annual (by age) Biennial (by age)		
Allen et al 2020[38]	US, 2018	CEA	Annual (20 years)	Lifetime horizon, use RCT data, some validation against RCT data	No discount rate reported, unclear if considers overdiagnosis, lead- or length-time bias, few sensitivity analyses
Criss et al 2019[17]	US, 2018	CUA	Annual (by age)	45-year time horizon, reports results from 4 different CISNET models	Few details on individual models
Du et al 2020[18]	Netherlands, 2020	CEA	Annual (by age) Biennial (by age)	Lifetime horizon, LDCT accuracy from published literature, considers impacts of LDCT radiation exposure, validated against RCT data	Unclear if considers overdiagnosis, lead- or length-time bias

Jaine et al 2020[39]	New Zealand, 2011	CUA	Biennial	Lifetime horizon, use RCT data, considers overdiagnosis and lead-time bias, costs of incidental findings	No consideration of length-time bias, impacts of LDCT radiation exposure not considered
Toumazis et al 2019[19]	US, 2019	CUA	Annual (by age) Biennial (by age)	Lifetime horizon, allows for overdiagnosis, lead-time and length bias	Limited detail of model, generalisability of results not discussed
Veronesi et al 2020[40]	Italy, 2018	CUA CEA	Annual (5 years)	Use RCT data, considers lead-time bias	5 year time horizon, no mention of overdiagnosis
Hofer et al 2018[20]	Germany, 2016	CUA CEA	Annual (by age) Biennial (by age)	15 year time horizon, use RCT data	No mention of overdiagnosis, lead- or length-time bias
Guzman et al 2020[41]	Spain, Unclear	CBA	Annual (3 years)	Use RCT data	<10 year time horizon, no consideration of overdiagnosis, lead- or length-time bias,

					few sensitivity analyses

CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; NR, not reported

*Few sensitivity analyses corresponds to <5 parameters assessed for their sensitivity

Modelling approach

One study reports a CBA[41], where health benefits from the different strategies are defined and compared in monetary terms. The other studies report either CEAs (n=12), CUAs (n=13) or both (n=9). In CEAs, the health benefits are defined by a single health outcome, with LYs gained the most commonly used health outcome in the 21 CEAs. In the CUAs, health benefits are defined as QALYs. The main strengths and weaknesses with the modelling approaches are summarized in Table 1 (also see Appendix 5).

Model structure and effectiveness evidence

The model types included decision tree approaches, cohort, and individual-level microsimulation models (see
Table 2). Most capture the impact of screening as a stage shift at diagnosis, where screen-detected lung cancers are diagnosed at earlier stages than lung cancers diagnosed in unscreened populations. To achieve this, models either explicitly assume a stage shift and quantify that shift as an input to the model, or they model the natural history of lung cancer with screening which implicitly leads to a stage shift.

Twelve studies use a decision tree modelling approach where effectiveness evidence is extrapolated using local data. Most (n=11) explicitly assume a stage shift at diagnosis for the LDCT screening arm. Guzman et al[41] assume more cases are detected with LDCT screening than no screening using data from NLST. The two US studies by Marshall et al[22,23] use the same decision tree approach. Three UK-based studies use a very similar approach to each other [27,30,35].

Re-analyses of individual participant data from NLST are conducted by two studies[29,37], thus have an implicit stage shift at diagnosis. The US study[29] uses SEER data to extrapolate beyond the NLST data, while the Australian study[37] follows a similar approach using data from Australian lifetables to extrapolate.

Table 2 Modelling methods and data used in the included studies

Modelling approach	Model name (if applicable)	How LDCT screening effectiveness incorporated into modelling	Effectiveness evidence used	Lung cancer stages modelled	Study
Decision tree		Explicit stage shift at diagnosis	NLST	I, II, IIIA, IIIB, IV	1 (Yang[34])
				Localised (I & II), regional (III), distant (IV)	1 (Goulart[28])
			ELCAP	I, II, IIIA, IIIB, IV	3 (Marshall[22,23]Wisnivesky[25])

			Early, Late	1 (Whynes[27])
		UK pilot studies	I, II, III, IV	2 (Field[30] Hinde[35])
		Israeli study	MECC I (I), MECC II (II-III), MECC III (IV)	1 (Shmueli[4])
		Japanese study	Early, Late	1 (Tabata[21])
		COSMOS	IA, IB, II, III, IV	1 (Veronesi[40])
	More screen-detected cases	NLST	Surgical vs medical treatment	1 (Guzman[41])
Re-analysis of trial data	Explicit modelling of participant-level data	NLST	I, II, III, IV	1 (Wade[37])
			IA, IB, II, III, IV	1 (Black[29])
Markov model	Explicit stage shift at diagnosis	NLST	Curative (stage IA – IIB plus IIIA with surgery), noncurative (IIIB without surgery, IIIB & IV)	1 (Cressman[32])
			Localised, regional, distant	1 (Jaine[39])
			IA, IB, II, IIIA, IIIB, IV	1 (Allen[38])
		ITALUNG/LUSI	I, II, IIIA, IIIB, IV	1 (Hofer[20])

			Weighted average from studies	I, II, IIIA, IIIB, IV	1 (Manser[26])
			Hypothetical	Localised (IA & IB receiving curative treatment), Advanced (all other stages)	1 (Mahadevi[5])
Cohort model		Explicit stage shift at diagnosis	ELCAP	A (IA, IB; localised), B (IIA, IIB, IIIA; regional), C (IIIB, IV; distant).	1 (Pyenson 2012[13])
			NLST and ELCAP	A (IA, IB; localised), B (IIA, IIB, IIIA; regional), C (IIIB, IV; distant).	2 (Pyenson 2014[12] Villanti[14])
			Unclear	Local & surgery, local & other, regional & single, regional & multiple, distant & single, distant & multiple	1 (Chirikos[24])
Multistate IPD model		Explicit modelling of participant-level data	NLST	No assumptions on stages	1 (Kumar[36])
Microsimulation model	OncoSim/ Cancer	Stage shift at diagnosis	NLST	I, II, III, IV	2 (Goffin[11,31])

	Risk Management model				
	Adapted SiMRiSc	Stage shift at diagnosis	Xie 2012[43] Sverzellati 2016[44]	TNM, with diameter as a proxy for size (T)	1 (Du[18])
	MISCAN-Lung*	Stage shift at diagnosis	NLST/PLCO	IA, IB, II, IIIA, IIIB, IV	3 (ten Haaf[15] Tomonaga[16] Criss[17])
	Lung Cancer Policy Model*	Explicit modelling of participant-level data	NLST/PLCO	I, II, IIIA, IIIB, IV	2 (McMahon[6] Criss[17])
	Unnamed	Reduced mortality for LDCT screen-detected stage I & II cancers	Unclear	I, II, III, IV	1 (Treskova[33])
	UM-LCSc (UoMichigan Lung Cancer screening model)*	Stage shift at diagnosis	NLST/PLCO	IA1, IA2, IB, II, IIIA, IIIB, and IV	1 (Criss[17])
	Lung Cancer Outcomes	Stage shift at diagnosis	NLST/PLCO	Early, Late	1 (Toumazis[19] Criss[17])

	Simulator (LCOS)*				
	Discrete event simulation model	Explicit modelling of participant-level data	NLST	IA, IB, IIA, IIB, IIIA, IIIB, IV	1 (Snowsill[3])

*CISNET registered

Six studies report a Markov model[5,20,26,32,38,39], another three use the same cohort model[12-14], with a further cohort model reported[24]. These all assume an explicit stage shift at diagnosis for those with screen-detected lung cancers, and are either based on NLST[42], an average of study estimates or assume a hypothetical effect. A multistate regression model using individual participant data from NLST is also reported[36].

Eight microsimulation models have been used to model the cost-effectiveness of LDCT screening (see
Table 2). Four of these models, reported in five studies, are part of the NIH Cancer Intervention and Surveillance Modeling Consortium, and as such are registered with CISNET (Cancer Intervention and Surveillance Modeling Network):

- Lung Cancer Outcomes Simulator (LCOS)[43] used in two studies[17,19]
- Lung Cancer Policy Model (LCPM)[44] used in two studies[6,17]
- MISCAN-Lung[45] used in three studies[15-17]
- University of Michigan Lung Cancer screening model (UM-LCSc)[46] using in one study[17].

One study [17] evaluates LDCT screening from these four CISNET models, reporting the average model results. All have a lifetime horizon, use data from NLST and PLCO, and assume a stage shift at diagnosis.

Treskova et al[33] use a microsimulation model, consisting of a number of modules (similar to MISCAN-Lung[45]). A reduction in the probability of death is assumed for those simulated individuals who have a screen-detected cancer diagnosed in stages I or II and would have died in the no screening arm. Du et al[18] use a microsimulation model, an adaptation of the Simulation Model on Radiation Risk and cancer Screening (SiMRiSc), assuming a stage shift at diagnosis. The OncoSim (formerly the Cancer Risk Management Model) microsimulation model simulates development of lung cancer from birth until death[11,31].

Snowsill et al[3] use a natural history model based on NLST to simulate lung cancer progression. Estimates from the natural history model are inputs to a discrete event simulation (DES) model which estimates the costs and effects associated with different screening strategies. The model assumes a stage shift at diagnosis for screened-detected lung cancers.

Studies evaluating a single, or annual screen for 3 or 5 years, are more likely to use a decision tree modelling approach and not evaluate many, if any, other strategies. Studies evaluating annual screens over different age ranges are more likely to use microsimulation models and have multiple comparisons.

Modelled lung cancer stages

All studies use some definition of cancer stage and/or intervention to model lung cancer survival. Eighteen studies use the number staging system, modelling the four stages (I, II, III, IV), with many modelling sub-stages. Six studies model three lung cancer stages, referred to generally as localised, regional and distant. Five of these studies provide details on how the

three stages relate to the number staging system, and there is variation between these. Only one study used the TNM staging system to model survival with lung cancer[18]. Three studies model only two lung cancer stages: early vs late[19,21,27]. The remaining studies combine treatment type into their lung cancer stage definitions[5,24,32].

Two studies do not model stages, instead refer only to whether patients are receiving surgical or medical treatment[41], or model the individual participant data from NLST[36].

Assumed all-cause mortality

The population of current/former smokers modelled in these studies are at higher risk of all-cause mortality compared to the general population. Therefore, assumptions on all-cause mortality should take this into account to avoid overestimation of non-lung cancer survival. Such overestimation would lead to an overestimation of the effectiveness of LDCT screening programmes (by assuming that those simulated individuals "cured" due to screening have a longer life than they actually would).

Of the studies modelling mortality, 18 report some accounting of this higher risk of all-cause death[3,5,6,12,14-16,18-20,26,29,33,35-37,39,40]. Many use all-cause mortality data adjusted for smoking behavior/history, as well as age, gender and/or race. One study[35] use area-specific survival rates (Manchester, UK) to account for the increased mortality associated with deprivation in that area (a proxy for smoking behavior).

Of the 13 studies[4,13,21-25,27,30,32,34,38,41] that do not adjust for smoking history, only one[34] acknowledged that this omission is likely to lead to more favourable findings for LDCT screening. The data used to inform all-cause mortality are not reported in two studies[11,31]. Those not reporting adjustment for high-risk of all-cause death in their populations are more likely to use decision tree models and address one specific policy question.

Potential harms

Six studies directly account for overdiagnosis through their natural history model, reporting overdiagnosis as an output[3,6,15,16,19,33]. Eleven studies report addressing overdiagnosis in the basecase analysis[4,5,11,13,21,26,28-30,36,39], with another 3 studies considering this in sensitivity analyses[12,25,32]. Nine of these studies reported inflating the number of cancers detected in the LDCT arm by a certain proportion above that in the control arm[4,11-13,21,25,26,28,39], ranging from 10% to 50%, with one using actual numbers of overdiagnosed cases directly from NLST[29]. One study had a separate health state in their model for overdiagnosis[5]. Another reports that adjustments are made for overdiagnosis, but details are not reported[32].

Although not reporting explicit adjustment for overdiagnosis, two studies[22,30] report adjusting for lead-time bias, and state that this addresses overdiagnosis. Since individuals with a long lead-time, who die before their cancer would have been clinically detected, would be described as "over-diagnosed" through screening, adjustment for lead-time bias does address overdiagnosis to some extent. However, as there is heterogeneity in when cancers present clinically, there should be heterogeneity in lead-time, including some very long lead-times, for overdiagnosis to be adequately addressed. Five further studies, not explicitly adjusting for overdiagnosis, adjust for lead-time bias[14,27,34,35,40]. One study adjusts for overdiagnosis by allowing patients in the LDCT screening arm to transition more quickly to a lung cancer diagnosis than those in the no-screening arm, but more slowly from diagnosis to death[36]. Four studies mentioned overdiagnosis as a potential limitation overestimating survival for the LDCT screening arm, but did not explicitly address it in the modelling[20,23,24,34]. The models attempting to address overdiagnosis, are less likely to overestimate the cost-effectiveness of LDCT screening.

Four studies incorporated potential increased radiation risk associated with LDCT compared to the control arm. They either incorporated deaths[33] or costs[34] from radiation-induced cancers, estimated excess relative risks for lung cancer per Gray exposure[6], or included a

module for the risk of radiation-induced tumours including associated costs and health effects[18].

Incidental findings

Five studies account, to some extent, for the costs of incidental findings from the LDCT arm[15,29,32,37,39]. Four studies assume costs for dealing with (non-specific) incidental findings[29,32,37,39], and one includes costs for "non-lung cancer surgery for potentially benign disease"[15]. Although only costs were included in these analyses, one could assume some clinical benefit of investigations for incidental findings. Eight studies are explicit that their model does not account for incidental findings[3,5,6,19,28,30,32,36]. The remaining studies do not mention incidental findings.

Lead-time and length bias

Fifteen studies report adjustments to account for lead-time bias[4,5,11-14,25-27,30,31,34,35,39,40], consisting of decreasing survival for screen-detected cancers in the LDCT-arm by a certain amount compared to survival for cancers detected in the non-LDCT arm. In seven studies, a pre-defined "lead-time" is reported for basecase and/or sensitivity analyses, ranging from six months[39] to eight years[27]. In other studies the "lead-time" is based on stage and/or age at diagnosis[3,30,34,35]. It is unclear how Pyenson et al[13] adjust for lead-time bias, they report assuming a "zero-year offset". In Marshall et al[22,23] the impact of potential lead-time bias was explored in sensitivity analyses by decreasing survival in simulated individuals with screen-detected cancer by one year. In six studies, lead-time bias is inherently accounted for in their natural history models and reported as a model outcome[3,6,15,16,19,33]. The remaining studies do not mention lead-time bias[15,16,18-21,24,28,29,32,33,36-38,41].

Three studies report considering length bias, however the details are not clear for one[11]. One study reports that they allow for the possibility that some cancers are extremely slow

progressing[5], the other allowed individuals in the LDCT arm to transition more quickly to lung cancer diagnosis than those in control arm, but transition to lung cancer death was modelled to be slower[36]. Studies with a natural history model account for length bias. One study acknowledges omission of adjusting for this bias is a limitation of their model and that survival in the LDCT arm will be overestimated[23].

Model validation and critical appraisal

Fourteen articles reported detail on model validation. Eleven conducted external validation against trial and registry data [6,11,15-19,31,33,34,38]. Two studies[29,36] report looking at internal consistency, and another reports assessment of face validity of the model, and approaches for quality assurance[3].

Most studies satisfied many of the critical appraisal criteria (see Appendix 6), including having a clearly defined question, population and comparator(s); an appropriate perspective and discount rate; and have considered, measured and valued the main cost items (LDCT scans, follow-up testing and lung cancer management costs).

Nineteen studies[3,6,11,12,15-17,19,20,29,31,32,34,36-41] were deemed to have an appropriate study design. For those that did not, it was due to the main source of evidence not being trials. This affected the older studies that were published before publication of the main effectiveness trials. The time horizon implemented in models ranged from 1 year to lifetime (see Modelling methods table). Twenty-five studies were assumed to have an appropriate time horizon of 10 years or more. Those studies with a short time horizon[22,23,28,40] are unlikely to capture all relevant health outcomes and costs. Twenty studies considered important outcomes (including lung cancer diagnoses and deaths, life-years), and most were deemed to have

appropriately measured those outcomes. The recent studies were more likely to discuss the generalizability of their results to other settings (n=17).

Only a third of studies (n=11) were deemed to have undertaken sufficient sensitivity analyses (≥ 5 parameters assessed). These were generally the more recent studies, with notable exceptions[4,5,26]. Ten studies clarified that there were no conflicts of interest, and one discussed ethical and distributional issues. Further details are given in Appendix 6.

The more recent studies (published in the last 5 years), tended to meet more of the critical appraisal criteria, and be more likely to consider overdiagnosis, length and lead-time bias, and the higher all-cause mortality associated with the modelled populations. Exceptions to this are a Markov model set in the US[5], and a CISNET registered model (LCPM) designed specifically to evaluate CT screening for lung cancer in a US population[6].

Discussion

Thirty-five studies were identified that reported modelling to evaluate the cost-effectiveness of LDCT screening for lung cancer compared to no, or another type of, screening. Studies sought to evaluate whether single (one-off), annual, biennial and/or triennial LDCT screening strategies were more cost-effective. Methodological approaches varied, including the model type, the definitions and number of lung cancer stages modelled, and time horizons. More complex models generally compared multiple policy questions, and considered the potential for harms and biases, such as overdiagnosis and lead-time bias. More recent models, which were often the more complex models, met many of the critical appraisal criteria.

This is an updated systematic review, following a pre-specified protocol. Additional items from studies included in the original systematic review have been extracted to more

thoroughly describe the multiple different modelling approaches taken. The review has been limited by incomplete reporting of some models, although more recent articles provide much detail in supplementary files. The items we chose to focus on were based on discussions around modelling LDCT lung cancer screening lung cancer that our group had with clinical and methodological experts. We did not extract detail on other potential sources of variability, such as the types of resource use and costs included, so our review is limited in that respect.

Economic evaluations can be incredibly helpful in the decision-making process. However, the impact of different approaches should be considered when interpreting and comparing model results. There are important differences between the approaches taken across the published studies. These differences can lead to over- or under-estimation of the cost-effectiveness of LDCT screening for lung cancer, where over-estimation would lead to an ICER that is biased downward, and under-estimation would lead to an ICER biased upward. A particular example is overdiagnosis, where RCT evidence is available to help inform the modelling (unlike, say, radiation exposure where impacts on patient-related outcomes is not described). A number of studies considered overdiagnosis in their modelling, but the approaches differed, from explicitly inflating the number of screen-detected cancers to the modeling of the raw data from the RCT which implicitly leads to overdiagnosis being a part of the model. Moreover, when similar approaches were used, the proportion of excess cancers differed across studies, from 10% to 50% more cancers in the LDCT screening arm. Some of these assumptions are likely to lead to underestimates of the cost-effectiveness of LDCT screening (by assuming high proportions of overdiagnosis). However, in other studies the issue of overdiagnosis was not addressed, therefore leading to likely overestimates of the cost-effectiveness of LDCT screening.

Many modelling assumptions/parameters are likely to have more than one possibility, so thorough evaluation of the uncertainty in models needs to be understood in the interpretation of the results. It is therefore noteworthy that only a third of models were deemed to have conducted sufficient sensitivity analyses.

There are still many uncertainties in modelling the cost-effectiveness of LDCT screening for lung cancer, many relating to available evidence. On-going data collection and analysis will help address some of these, for instance as the RCT evidence matures, we may get a clearer sense of the extent of overdiagnosis and impacts on all-cause mortality. Future research could also focus on the patient impacts of reporting incidental findings from LDCT screening. But there is still the issue of what modelling approach to take and how the different approaches impact on results.

Modelling lung cancer screening is not straightforward. Economic evaluations addressing some of the most important issues will necessarily be complex. We found that approaches incorporating natural history models addressed many of the critical appraisal items. However, these are difficult to do and should be extensively validated.

A “best” model to capture and explain the level of uncertainty in this area is not realistic. Given that so many decisions go into the development of model-based economic evaluations, variation in approach can be helpful, insofar as these differences can be explored when estimating cost-effectiveness. Using multiple models to evaluate the same policy question, as done with some of the CISNET lung cancer screening models[17], can help provide insight on the impact of model differences. Many national policy-making bodies will not have the time or resources to do this. Therefore, insights from this review will be useful to ensure that the modelling-related choices made are consistent with the issues decision-makers believe to be important and relevant to their population and setting, in consultation with their key stakeholders.

Conclusion

Although thirty-five economic evaluations of LDCT screening for lung cancer have been conducted since 2000, the evidence on cost-effectiveness is not settled. Advocates and opponents of LDCT screening for lung cancer have both been able to point to peer-reviewed published economic evaluations justifying their position, but an understanding of why different models have produced such divergent results has been missing. By clearly identifying a number of key methodological issues and evidence needs for future economic evaluations, steps towards this can be achieved.

References

1. Yang H, Varley-Campbell J, Coelho H, et al. Do we know enough about the effect of low-dose computed tomography screening for lung cancer on survival to act? A systematic review, meta-analysis and network meta-analysis of randomised controlled trials. Diagn Progn Res. 2019;3:23.

2. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med. 2020;382(6):503-513.

3. Snowsill T, Yang H, Griffin E, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. Health Technol Assess. 2018;22(69):1-276.

4. Shmueli A, Fraifeld S, Peretz T, et al. Cost-effectiveness of baseline low-dose computed tomography screening for lung cancer: the Israeli experience. Value Health. 2013;16(6):922-931.

5. Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. JAMA. 2003;289(3):313-322.

6. McMahon PM, Kong CY, Bouzan C, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. J Thorac Oncol. 2011;6(11):1841-1848.

7. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. Value Health. 2012;15(6):804-811.

8. Jonas DE, Reuland DS, Reddy SM, et al. Screening for lung cancer with low-dose computed tomography: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2021;325(10):971-987.

9. Church TR, Black WC, Aberle DR, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med. 2013;368(21):1980-1991.

10. van de Wiel JC, Wang Y, Xu DM, et al. Neglectable benefit of searching for incidental findings in the Dutch-Belgian lung cancer screening trial (NELSON) using low-dose multidetector CT. Eur Radiol. 2007;17(6):1474-1482.

11. Goffin JR, Flanagan WM, Miller AB, et al. Cost-effectiveness of lung cancer screening in Canada. JAMA Oncol. 2015;1(6):807-813.

12. Pyenson BS, Henschke CI, Yankelevitz DF, Yip R, Dec E. Offering lung cancer screening to high-risk medicare beneficiaries saves lives and is cost-effective: an actuarial analysis. Am Health Drug Benefits. 2014;7(5):272-282.

13. Pyenson BS, Sander MS, Jiang Y, Kahn H, Mulshine JL. An actuarial analysis shows that offering lung cancer screening as an insurance benefit would save lives at relatively low cost. Health Aff. 2012;31(4):770-779.

14. Villanti AC, Jiang Y, Abrams DB, Pyenson BS. A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. PLoS One. 2013;8(8):e71379.

15. ten Haaf K, Tammemägi MC, Bondy SJ, et al. Performance and cost-effectiveness of computed tomography lung cancer screening scenarios in a population-based setting: a microsimulation modeling analysis in Ontario, Canada. PLoS Med. 2017;14(2):e1002225.

16. Tomonaga Y, ten Haaf K, Frauenfelder T, et al. Cost-effectiveness of low-dose CT screening for lung cancer in a European country with high prevalence of smoking - a modelling study. Lung Cancer. 2018;121:61-69.

17. Criss SD, Cao P, Bastani M, et al. Cost-effectiveness analysis of lung cancer screening in the United States: a comparative modeling study. Ann Intern Med. 2019;171(11):796-804.

18. Du Y, Sidorenkov G, Heuvelmans MA, et al. Cost-effectiveness of lung cancer screening with low-dose computed tomography in heavy smokers: a microsimulation modelling study. Eur J Cancer. 2020;135:121-129.

19. Toumazis I, Tsai EB, Erdogan SA, et al. Cost-effectiveness analysis of lung cancer screening accounting for the effect of indeterminate findings. JNCI Cancer Spectr. 2019;3(3):pkz035.

20. Hofer F, Kauczor HU, Stargardt T. Cost-utility analysis of a potential lung cancer screening program for a high-risk population in Germany: a modelling approach. Lung Cancer. 2018;124:189-198.

21. Tabata H, Akita T, Matsuura A, et al. Cost-effectiveness of the introduction of low-dose CT screening in Japanese smokers aged 55 to 74 years old. Hiroshima J Med Sci. 2014;63(1-3):13-22.

22. Marshall D, Simpson KN, Earle CC, Chu CW. Economic decision analysis model of screening for lung cancer. Eur J Cancer. 2001;37(14):1759-1767.

23. Marshall D, Simpson KN, Earle CC, Chu C. Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort. Lung Cancer. 2001;32(3):227-236.

24. Chirikos TN, Hazelton T, Tockman M, Clark R. Screening for lung cancer with CT: a preliminary cost-effectiveness analysis. Chest. 2002;121(5):1507-1514.

25. Wisnivesky JP, Mushlin AI, Sicherman N, Henschke C. The cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. Chest. 2003;124(2):614-621.

26. Manser R, Dalton A, Carter R, Byrnes G, Elwood M, Campbell DA. Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting. Lung Cancer. 2005;48(2):171-185.

27. Whynes DK. Could CT screening for lung cancer ever be cost effective in the United Kingdom? Cost Eff Resour Alloc. 2008;6:5.

28. Goulart BH, Bensink ME, Mummy DG, Ramsey SD. Lung cancer screening with low-dose computed tomography: costs, national expenditures, and cost-effectiveness. J Natl Compr Canc Netw. 2012;10(2):267-275.

29. Black WC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. N Engl J Med. 2014;371(19):1793-1802.

30. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess. 2016;20(40):1-146.

31. Goffin JR, Flanagan WM, Miller AB, et al. Biennial lung cancer screening in Canada with smoking cessation-outcomes and cost-effectiveness. Lung Cancer. 2016;101:98-103.

32. Cressman S, Peacock SJ, Tammemagi MC, et al. The cost-effectiveness of high-risk lung cancer screening and drivers of program efficiency. J Thorac Oncol. 2017;12(8):1210-1222.

33. Treskova M, Aumann I, Golpon H, Vogel-Claussen J, Welte T, Kuhlmann A. Trade-off between benefits, harms and economic efficiency of low-dose CT lung cancer screening: a microsimulation analysis of nodule management strategies in a population-based setting. BMC Med. 2017;15(1):162.

34. Yang SC, Lai WW, Lin CC, et al. Cost-effectiveness of implementing computed tomography screening for lung cancer in Taiwan. Lung Cancer. 2017;108:183-191.

35. Hinde S, Crilly T, Balata H, et al. The cost-effectiveness of the Manchester 'lung health checks', a community-based lung cancer low-dose CT screening pilot. Lung Cancer. 2018;126:119-124.

36. Kumar V, Cohen JT, van Klaveren D, et al. Risk-targeted lung cancer screening: a cost-effectiveness analysis. Ann Intern Med. 2018;168(3):161-169.

37. Wade S, Weber M, Caruana M, et al. Estimating the cost-effectiveness of lung cancer screening with low-dose computed tomography for high-risk smokers in Australia. J Thorac Oncol. 2018;13(8):1094-1105.

38. Allen BD, Schiebler ML, Sommer G, et al. Cost-effectiveness of lung MRI in lung cancer screening. Eur Radiol. 2020;30(3):1738-1746.

39. Jaine R, Kvizhinadze G, Nair N, Blakely T. Cost-effectiveness of a low-dose computed tomography screening programme for lung cancer in New Zealand. Lung Cancer. 2020;144:99-106.

40. Veronesi G, Navone N, Novellis P, et al. Favorable incremental cost-effectiveness ratio for lung cancer screening in Italy. Lung Cancer. 2020;143:73-79.

41. Guzman R, Guirao À, Vela E, et al. Outcomes and cost of lung cancer patients treated surgically or medically in Catalunya: cost-benefit implications for lung cancer screening programs. Eur J Cancer Prev. 2020;29(6):486-492.

42. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409.

43. National Cancer Institute Cancer Intervention and Surveillance Modeling Network (CISNET). Lung Cancer Outcomes Simulator. https://resources.cisnet.cancer.gov/registry/packages/lcos-stanford/. Accessed 28th September 2020.

44. National Cancer Institute Cancer Intervention and Surveillance Modeling Network (CISNET). Lung Cancer Policy Model. https://resources.cisnet.cancer.gov/registry/packages/lcpm-mgh/. Accessed 28th September 2020.

45. National Cancer Institute Cancer Intervention and Surveillance Modeling Network (CISNET). MISCAN-Lung. https://resources.cisnet.cancer.gov/registry/packages/miscan-lung-erasmus/. Accessed 28the September 2020.

46. National Cancer Institute Cancer Intervention and Surveillance Modeling Network (CISNET). University of Michigan Lung Cancer Screening Model. https://resources.cisnet.cancer.gov/registry/packages/um-lcsc-michigan/. Accessed 28th September 2020.

Appendices

Appendix 1. Databases searched and search strategy for MEDLINE

Databases searched: Medline/Medline In Process, Embase, HMIC, Web of Science, EconLit, HERC (Health Economics Research Centre), CEA (Cost-Effectiveness Analysis) Registry

Search strategy for MEDLINE

Strategy:

1. exp Lung Neoplasms/
2. ((lung$ or bronch$ or pulmon$) adj3 (cancer$ or neopla$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or small cell or squamous)).ti,ab,ot,kw.
3. (NSLC or NSCLC or SLC or SCLC).ti,ab,ot,kw.
4. 1 or 2 or 3
5. exp Tomography, X-Ray Computed/
6. ((CT or CAT) adj3 (scan$ or screen$)).ti,ab,ot,kw.
7. ((computer$ adj3 tomogra$) and (scan$ or screen$)).ti,ab,ot,kw.
8. (tomogra$ or helix or helical or spiral$ or spiro$).ti,ab,ot,kw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. exp Economics/
12. Economics, Medical/
13. Economics, Nursing/
14. Economics, Pharmaceutical/
15. exp Economics, Hospital/
16. (economic$ or price or prices or pricing or priced or discount or discounts or discounted or discounting or ration$ or expenditure or expenditures or budget$ or afford$ or pharmacoeconomic$ or pharmaco-economic$).ti,kf.
17. exp "Fees and Charges"/
18. (fee or fees or charge$ or preference$).tw.
19. (fiscal or funding or financial or finance).tw.
20. exp "Costs and Cost Analysis"/
21. exp Health Care Costs/
22. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
23. (value adj2 (money or monetary)).ti,ab,kf.
24. exp Decision Support Techniques/
25. exp Models, Economic/
26. economic model*.ab,kf.
27. markov$.tw.
28. Markov Chains/
29. monte carlo.tw.
30. Monte Carlo Method/
31. (decision adj2 (tree$ or analy$ or model$)).ti,ab,kf.

32. exp Decision Theory/
33. (survival adj3 analy$).tw.
34. "Deductibles and Coinsurance"/
35. exp Health Expenditures/
36. Uncertainty/
37. exp Budgets/
38. or/11-37
39. Animals/ not human.sh.
40. 38 not 39

Appendix 2. Inclusion and exclusion criteria

Characteristic	Inclusion criteria	Exclusion criteria
Population	People at risk of lung cancer	People with existing cancer, clinically suspected lung cancer, or hereditary cancer syndromes
Interventions	LDCT (single or multiple screens)	
Comparator	No screening or screening with another imaging modality (including X-ray)	No comparator or screening with non-imagining modality
Study design	Cost-utility, cost-effectiveness, cost-benefit, cost-consequence analysis	Cost-minimisation analysis Where incremental analyses or possibility for their calculation are not reported Non-systematic reviews
Publication types	Full-text articles	Editorials, comments, letters, abstracts, non-English language articles

Appendix 3. Summary of cost-effectiveness results arranged by screening frequency and comparator

Table 1. Single LDCT screening vs no screening

Study	Country, Price year	Analysis	Eligible population	Model, Time horizon	Incremental effects and costs	ICER
Marshall[1]	US, 1999	CEA	General smokers aged 60–74 years "Very - high risk" General smokers aged 60–74 years	Decision tree model, 5 years	LYs: 4417 Costs: US$26M	US$5,940/LYG
Wisnivesky[2]	US, 2000	CEA	Adults aged ≥60 years with ≥10 pack-year smoking history	Decision tree, Unclear	LYs: 0.1 Costs: US$232	US$2,500/LYG
Whynes[3]	UK, 2004	CUA	Men aged 61 years at high risk	Decision tree, 40 years	QALYs: 0.01 Costs: £201	£13,910/QALY
McMahon[4]	US, 2006	CUA	Aged 50-70, 60-74, 70-74 with current & former =>20 pack-year history	Patient-level microsimulation (Lung Cancer Policy Model), Lifetime	QALYs: 0.009 to 0.022 Costs: US$1,778 to US$3,637	US$144,000 - $207,000/QALY
Shmueli[5]	Israel, 2012	CUA	Adults aged ≥45 years with ≥10 pack-year smoking history	Decision tree, Lifetime	QALYs: .06 Costs: US$86.47	US$1,464/QALY
Hinde[6]	UK, 2015	CUA	55-74yrs ever smokers with 6-year lung cancer risk of ≥1.51% (using $PLCO_{M2012}$)	Decision tree, Lifetime	QALYs: 65.85 Costs: £663,076	£10,069/QALY
Field[7]	UK, 2016	CUA	Adults aged 50–75 years, at =>5% risk of lung cancer according to the Liverpool Lung Project risk prediction model	Decision tree, Lifetime	QALYs: 66.8 Costs: £565,498	£8466/QALY
Snowsill[8]	UK, 2016	CUA	Aged 55 - 80 years (current or former smokers), with 3%, 4% or 5% risk of lung cancer (based on Liverpool Lung Project risk prediction model)	Discrete event simulation model (informed by natural history model), Lifetime	QALYs: 0.0008 to 0.0001 Costs: £23 to £32	3 single screen scenarios were on the efficient frontier. £28,169/QALY to £30,821/QALY depending on eligible population

Table 2. Annual LDCT screen for 3 years vs no screening

Study	Country, Price year	Analysis	Eligible population	Model, Time horizon	Incremental effects and costs	ICER
Goffin 2015[9]	Canada, 2008	CUA	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	Microsimulation model (OncoSim), 20 years	QALYs: 32,000 Costs: Can$2.3Billion	Can$74,000/QALY (100% are NLST eligible)
Black[10]	US, 2009	CEA CUA	NLST cohort (aged 55–74 years with ≥ 30 pack-year smoking history)	Decision tree, Lifetime	Costs: US$1,631 LYs: 0.0316 QALYs: 0.0201	US$52,000/LY US$81,000/QALY
Goulart 2012	US,	CEA	Unclear. Assume as for NLST.	Decision tree, 1 year	LC deaths avoided: 5,428 Costs: US$1,303M	US$240,081/LC death avoided
Cressman[11]	Canada, 2015	CUA	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	Markov, 30 years	QALYs: 0.032 Costs: Can$668	Can$20,724/QALY
Wade[12]	Australia, 2015	CEA CUA	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	Decision tree, 10 years	LYs: 0.0113 QALYs: 0.0067 Costs: AUS$1564	AUS$138,000/LY AUS$ 233,000/QALY
Snowsill[8]	UK, 2016	CUA	Aged 55 - 80 years (current or former smokers), with 3%, 4% or 5% risk of lung cancer (based on Liverpool Lung Project risk prediction model)	Discrete event simulation model (informed by natural history model), Lifetime	QALYs: 0.0012 Costs: £48	Only one strategy on the efficient frontier. ICER (vs no screening): £40,034/QALY
Guzman	Spain, Unclear	CBA	As NLST	Decision tree, 10 years		"cost-benefit ratio will break even between 3 (for 2% incidence) and 6 years (for 1% incidence) after launch" With healthcare cost savings thereafter

Table 3. Annual LDCT screen for 5 years vs no screening

Study	Country, Price year	Analysis	Eligible population	Model, Time horizon	Incremental effects and costs	ICER
Chirikos[13]	US, 2000	CEA	Adult smokers aged 45–74 years	Cohort model, 15 years	LYs: 2.245 Costs: US$75,336 LYs: 0.856 Costs: US$77,059	US$33,557–90,022/LYG
Manser[14]	Australia, 2002	CUA CEA	Male current smokers aged 60–64 years. Sens analyses 65-69yrs, low and higher risk evaluated.	Markov model, 15 years	QALYs: NR LYs: 287 Costs: AU$16,486,239	AU$105,090/QALY AU$57,325/LYG
Marshall[15]	US, 1999	CUA CEA	'High-risk' adults aged 60–74 years	Decision tree model, 5 years	LYs: 5036 QALYs: NR Costs: US$96M	US$19,533/QALY US$18,968/LY
Treskova 2017[16]	Germany, 2016*	CEA	Start age 50-55 years, finish age 75-80 years, pack-years 15-40, cessation 9-15 years	Microsimulation model, Lifetime	LYS: 133,222 to 362,039 Costs: €2,232M to €7,556M	Efficient scenarios (per LYG) €16,754 to €20,870 Efficient scenarios (per lung cancer death averted) €155,287 - €203,792
Veronesi[17]	Italy, 2018	CUA CEA	Aged 55–79 years, current or former smokers of ≥30 pack-years who stopped<15 years prior to study	Decision tree model, 5 years	Costs: €255 QALYs: 0.08 LYs: 0.09	€3,297/QALY (US$3,884) [per person per year] €2,944/LYG (US$3,527) [per person per year]

*Price year assumed.

Table 4. Annual LDCT screen by specific age ranges vs no screening

Study	Country, Price year	Analysis	Eligible population	Model, Time horizon	Incremental effects and costs	ICER(s) vs no screening
Goffin 2015[9]	Canada, 2008	CUA	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	Microsimulation model (OncoSim), 20 years	QALYs: 51,000 and 95,000 Costs: CA$2.7Billion and CA$2.1Billion	CA$52,000/QALY and CA$56,000/QALY depending on eligible population
Mahadevia[18]	US, 2001	CUA	60-80 year-old heavy smokers (current and former, > 20 pack-years)	Markov model, 40 years	Current smokers QALYs: 0.039 Costs: US$4,600 Former smokers: QALYs: 0.020 Costs: US$4,300	Current smokers US$116,300/QALY Former smokers: US$2,322,700/QALY
McMahon[4]	US, 2006	CUA	Males/females aged 50-74 with current & former =>20 pack-year history	Patient-level microsimulation model (Lung Cancer Policy Model), Lifetime	NR	$110,000/QALY - $203,000/QALY depending on gender, age group and smoking history of eligible population.
Pyenson 2012[19]	US, 2012	CEA	smokers and former smokers ages 50–64, with at least 30 pack-years of smoking each	Cohort model, 15 years	LYs: 130,195 Costs: NR	US$18,862/LYG
Pyenson 2014[20]	US, 2014	CEA	smokers and former smokers aged 55 to 80 years who had a ≥30 pack-year smoking history and had smoked within the previous 15 years	Cohort model, 20 years	LYs: 2,257,053 Costs: 41,647,811,614	US$18,452/LYG
ten Haaf[21]	Canada, 2015	CEA	10-40 pack-years. 10 - 20 years since smoking cessation.	Microsimulation model (MISCAN-Lung), Lifetime	LYs: 1,276 to 3,214 Costs: $49,768,886 to $206,703,139	Can$39,000/LY to Can$64,500/LY depending on age and smoking history of eligible population*
Tomonaga[22]	Switzerland, 2015	CEA	10-40 pack-years. 10-20 years since smoking cessation.	Microsimulation model (MISCAN-Lung), Lifetime	LYs: 2,111 to 3,897 Costs: €64,127,788 to 188,515,091	€30,500/LY to €48,500/LY depending on age and smoking history of eligible population*

Villanti[23]	US, 2012	CUA	Aged 50 - 64 years, with 30+ pack-years of smoking history.	Cohort model, 15 years	QALYs: 985,284 (ELCAP), 722,795 (NLST) Costs: US$27,824,282,242 (ELCAP), US$34,054,299,361 (NLST)	US$28,240/QALY based on ELCAP data, US$47,115/QALY based on NLST data
Criss[24]	US, 2018	CUA	As NLST, stopping at ages 74, 77 or 80 years	4 microsimulation models: MISCAN-Lung, Lung Cancer Policy Model, UMLCSc, Lung Cancer Outcomes Simulator, 45 years	QALYs: 1,990 to 2,140 Costs: $87M to $98M	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)
Du[25]	Netherlands, 2020	CEA	Male and female current smokers of at least 20 cigs/day	Microsimulation model (Simulation Model on Radiation Risk and cancer Screening (SiMRiSc)), Lifetime	Costs: €230.6M to €281.0M LYs: 8,218 to 8,741	€27,600/LYG - €32,400/LYG depending on gender and age of eligible population
Toumazis[26]	US, 2019	CUA	20-40 pack-years.10-20 years smoking cessation	Microsimulation model (LCOS), Lifetime	QALYs: 0.0161 to 0.0193 Costs: $903 to $2,391	US$55,968/QALY – US$124,147/QALY depending on age and smoking history of eligible population and whether disutility for indeterminate results included
Hofer[27]	Germany, 2016	CUA CEA	Aged 55 to 75 years, former and current smokers (≥20 cigarettes per day)	2 Markov models, one for natural history, one for treatment & beyond, 15 years	QALYs: 0.04 LYs: 0.06 Costs: €1,153	€30,291/QALY €19,302/LYG
Snowsill[8]	UK, 2016	CUA	Aged 55 - 80 years (current or former smokers), with 3%, 4% or 5% risk of lung cancer (based on Liverpool Lung Project risk prediction model)	Discrete event simulation model (informed by natural history model), Lifetime	-	No strategies on the efficiency frontier.

* only reflects ICERs vs no screening for the annual screening strategies on the efficiency frontier

Table 5. Biennial LDCT screen for specific age ranges vs no screening

Study	Country, Price year	Analysis	Eligible population	Model, Time horizon	Incremental effects and costs	ICER
Jaine[28]	New Zealand, 2011	CUA	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	Markov model, Lifetime	QALYs: 3,567 Costs: $221	NZ$65,000/QALY for total cohort [NZ$30,000/QALY to NZ$89,000/QALY depending on gender, age and ethnicity of eligible population]
Toumazis[26]	US, 2019	CUA	30-40 pack-years, 10-15 years smoking cessation.	Lung Cancer Outcomes Simulator (LCOS), Lifetime	QALYs: 0.0065 to 0.0134 Costs: $282 to $1,033	US$43118/QALY – US$76909/QALY depending on age and smoking history of eligible population, and inclusion of disutility for indeterminate results
Hofer[27]	Germany, 2016	CUA CEA	Aged 55 -75 years, former and current smokers (≥20 cigarettes per day)	2 Markov models, one for natural history, one for treatment & beyond, 15 years	NR	€38,694/QALY €24,594/LYG
ten Haaf[21]	Canada, 2015	CEA	Multiple definitions: up to 40 pack-years, up to 20 years since smoking cessation	Microsimulation model (MISCAN-Lung), Lifetime	-	No biennial strategies were on the efficiency frontier (only annual strategies)
Tomonaga[22]	Switzerland, 2015	CEA	30-40 pack-years.	Microsimulation model (MISCAN-Lung), Lifetime	LYs: 1,265 to 1,987 Costs: €32,447,039 to €61,004,514	€25,500/LYG to €31,000/LYG depending on age and smoking history of eligible population
Du[25]	Netherlands, 2015	CEA	Male and female current smoker of at least 20 cigs/day	Microsimulation model (Simulation Model on Radiation Risk and cancer Screening (SiMRiSc)), Lifetime	LYs: 4,854 to 6,776 Costs: €86.3M to €143.2M	€17,700/LYG - €21,100/LYG depending on gender and age of eligible population
Snowsill[8]	UK, 2016	CUA	Aged 55 - 80 years (current or former smokers), with 3%, 4% or 5% risk of lung cancer (based on Liverpool Lung Project risk prediction model)	Discrete event simulation model (informed by natural history model), Lifetime	-	No strategies on the efficiency frontier.

Table 6. Triennial LDCT screen for 20 years vs annual LDCT screen for 20 years

Study	Country, Price year	Analysis	Eligible population	Model, Time horizon	Incremental effects and costs	ICER
Tomonaga[22]	Switzerland, 2015	CEA	30-40 pack-years.	Microsimulation model (MISCAN-Lung), Lifetime	LYs: 1,217 Costs: €33,324,475	€27,374/LY

Table 7. Biennial LDCT screen for 20 years vs annual LDCT screen for 20 years

Study	Country, Price year	Analysis	Eligible population	Model, Time horizon	Incremental effects and costs	ICER for annual vs biennial
Goffin 2016	Canada, 2008	CUA	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	Microsimulation model (OncoSim), Lifetime	QALYs: -19,000 to 0 Costs: -$1.2Billion to -$1Billion	CAN$54,000/QALY to $4.8M/QALY depending on estimates of sensitivity and specificity of LDCT

Table 8. Annual LDCT screen specific age ranges vs annual chest x-ray

Study	Country, Price year	Analysis	Eligible population	Model, Time horizon	Incremental effects and costs	ICER for LDCT vs CXR
Tabata	Japan	CEA	Smokers aged 55–74 years	Decision tree, Lifetime	LYs: 742 to 17,453 Costs: ¥730 to ¥22,473	¥268,000 to ¥1,942,000/LYG depending on gender and age

CXR, chest x-ray;

Table 9. Annual LDCT screen for 20 years vs annual MRI screen for 20 years

Study	Country, Price year	Analysis	Eligible population	Model, Time horizon	Incremental effects and costs	ICER for MRI vs LDCT
Allen 2020	US	CEA	60-year-old male and female smokers	Markov cohort model, Lifetime	LYs: 0.01 (males), 0 (females) Costs: -$2808 (males), -$3112 (females)	$258,169 /LYG (males) $403,888 /LYG (females)

Appendix 4. Summary of policy questions for each included study (sorted by year of publication)

Study, year	Country	LDCT screening strategy			Eligible population	Comparator	Perspective
		Frequency	Duration	Includes smoking cessation			
Marshall 2001[15]	US	Annual	5 years	No	'High-risk' adults aged 60–74 years	No screening	Healthcare payer
Marshall 2001 [1]	US	Single	NA	No	General smokers aged 60–74 years "Very - high risk" General smokers aged 60–74 years	No screening	Healthcare payer
Chirikos 2002[13]	US	Annual	5 years	No	Adult smokers aged 45–74 years	No screening	National payer
Mahadevia 2003[18]	US	Annual	Aged 60-80 years	No	60-80 year-old heavy smokers (current and former, > 20 pack-years)	No screening	Societal
Wisnivesky 2003[2]	US	Single	NA	No	Adults aged ≥60 years with ≥10 pack-year smoking history	No screening	Healthcare payer
Manser 2005[14]	Australia	Annual	5 years	No	Male current smokers aged 60–64 years. Sens analyses 65-69yrs, low and higher risk evaluated.	No screening	Government (third-party)
Whynes 2008[3]	UK	Single	NA	No	Men aged 61 years at high risk	No screening	Healthcare payer
McMahon 2011[4]	US	Single Annual Annual Annual	NA Aged 70-74 years Aged 60-74 years Aged 50-70 years	No	Aged 50-70, 60-74, 70-74 with current & former =>20 pack-year history (Sens analyses: current & former with ≥40 pack-year, current & former (<10 years) with ≥20 pack-year, current with ≥40 pack-year)	No screening	Societal
Goulart 2012[29]	US	Unclear. Suggests as in NLST.	Unclear. Suggests as in NLST.	No	NLST (smokers aged 55 to 74 years)	No screening	Healthcare payer and patient
Pyenson 2012[19]	US	Annual	Aged 50-64 years	No	smokers and former smokers ages 50–64, with at least 30 pack-years of smoking each	No screening	Healthcare payer
Shmueli 2013[5]	Israel	Single	NA	No	Adults aged ≥45 years with ≥10 pack-year smoking history	No screening	Healthcare payer
Villanti 2013[23]	US	Annual	Aged 50-64 years	Yes	Aged 50 - 64 years, with 30+ pack-years of smoking history	No screening	Commercial payer
Black 2014[10]	US	Annual	3 years	No	NLST cohort (aged 55–74 years with ≥ 30 pack-year smoking history)	No screening	Societal
Pyenson 2014[20]	US	Annual	Aged 55-80 years	No	smokers and former smokers aged 55 to 80 years who had a ≥30 pack-year smoking history and had smoked within the previous 15 years	No screening	Healthcare payer
Tabata 2014[30]	Japan	Annual	Aged 55-74 years	No	Smokers aged 55–74 years	CXR annual	Healthcare payer
Goffin 2015[9]	Canada	Annual	3 years Aged 55-74 years	Yes	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	No screening	Healthcare payer
Field 2016[7]	UK	Single	NA	No	Adults aged 50–75 years, at =>5% risk of lung cancer according to the Liverpool Lung Project risk prediction model	No screening	Healthcare payer
Goffin 2016[31]	Canada	Biennial	20 years	No	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	Annual LDCT screen over 20 years	Healthcare payer

Study, year	Country	LDCT screening strategy			Eligible population	Comparator	Perspective
		Frequency	Duration	Includes smoking cessation			
Cressman 2017[11]	Canada	Annual	3 years	No	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	No screening	Public payer
ten Haaf 2017[21]	Canada	Annual Biennial	Multiple as defined by age	No	10-40 pack-years. 10 - 20 years since smoking cessation.	No screening	Healthcare payer
Treskova 2017[16]	Germany	Annual	5 years	No	Age range 50-74, pack-years=>30, quit<=15yrs; Age range 55-80, pack years=>30, quit<=15yrs; Age range 50-75, pack-years=>15, quit<=9yrs; Age range 55-75, pack-years=>40, quit<=10yrs	No screening	Healthcare payer
Yang 2017[32]	Taiwan	Annual	3 years	No	Adults aged 55-75 years with ≥30 pack-years	Chest x-ray (annual for 3 years)	Public payer
Hinde 2018[6]	UK	Single	NA	No	55-74yrs ever smokers with 6- year lung cancer risk of ≥1.51% (using $PLCO_{M2012}$)	No screening	Healthcare payer
Hofer 2018[27]	Germany	Annual (Biennial, and semi-Annual in sensitivity analyses)	Aged 55- 75 years	No	former and current smokers (≥20 cigarettes per day)	No screening	Public payer
Kumar 2018[33]	US	Annual	3 years	No	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	Chest x-ray (annual for 3 years)	Healthcare payer
Snowsill 2018[8]	UK	Single Annual Biennial	NA 3 years Until 80 years old Until 80 years old	No	Aged 55 - 80 years with a history of smoking (i.e. current or former smokers), with 3%, 4% or 5% risk of lung cancer (based on Liverpool Lung Project risk prediction model)	No screening	Healthcare payer
Tomonaga 2018[22]	Switzerland	Annual Biennial Triennial	Multiple as defined by age	No	10-40 pack-years. 10-20 years since smoking cessation.	No screening	Healthcare payer
Wade 2018[12]	Australia	Annual	3 years	No	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	No screening	Healthcare payer

Study, year	Country	LDCT screening strategy			Eligible population	Comparator	Perspective
		Frequency	Duration	Includes smoking cessation			
Criss 2019[24]	US	Annual	Aged 55 years until: 74 years 77 years 80 years	No	NLST, stop screening at age: 74 years (as in NLST), 77 years (as for CMS), 80 years (as for USPSTF)	No screening	Healthcare payer
Toumazis 2019[26]	US	Annual Biennial	Start ages of 50, 55, 60 and 65 years. Stop ages of 70, 75 and 80 years.	No	Men and women smoking exposure between 20, 30, and 40 packyears, and 10, 15, and 20 years since smoking cessation for former smokers.	No screening	Single payer/insurer
Allen 2020[34]	US	Annual	20 years	No	60-year-old male and female subjects with a smoking burden of two packs (40 cigarettes) per day since age 42 (18 years × 2 packs per day = 36 pack years at time-0). (Analysed male and female cohorts separately)	MRI	Healthcare payer
Du 2020[25,35]	Netherlands	Annual Biennial	Start ages of 50, 55 & 60 years. Stop ages of 75, 80 & 85 years.	No	Male and female current smoker of at least 20 cigs/day	No screening	Health insurance
Guzman 2020[36]	Spain	(As NLST) Annual	3 years	No	As NLST	No screening)	Healthcare payer
Jaine 2020[28]	New Zealand	Biennial	20 years	No	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	No screening	Healthcare payer
Veronesi 2020[17]	Italy	Annual	5 years	No	Aged 55–79 years, current or former smokers of ≥30 pack-years who stopped<15 years prior to the study	No screening	Tax payer

Appendix 5. Summary of modelling methods (sorted by year of publication)

Authors	Analysis Health outcome	Time horizon Discount Rate	Model type (and stage definitions)	How modelled benefit of screening Effectiveness evidence	How modelled risk of non-LC mortality Accounted for higher risk than non-smoking general population?	Overdiagnosis	Lead-time bias	Length time bias	Incidental findings	Radiation exposure	Model performance / validation
Marshall 2001[15]	CUA CEA (life-years)	5 years 3%	Decision tree model – based on SEER data and ELCAP data. Modelled stage I*, stage II, stage IIIA, stage IIIB and stage IV for mortality *further subdivided according to tumour size (≤10 mm, 11–20 mm, 21–45 mm, >45 mm)	Stage shift at diagnosis. Data from ELCAP.	No. Expected rates of survival for the general population were those for the 1990 US population standardised by sex, age group and race.	In sensitivity analyses decreased survival for LDCT-screened detected cancers by 1yr as a proxy for the impact of overdiagnosis and lead-time bias	In sensitivity analyses decreased survival for LDCT-screened detected cancers by 1yr as a proxy for overdiagnosis and lead-time bias.	NR	NR	NR	NR
Marshall 2001[1]	CEA (life-years)	5 years 3%	Decision tree model based on SEER and ELCAP. Same as Marshall 2001[15]	Stage shift at diagnosis. Data from ELCAP.	No. Standardized by gender, age group and race	No	In sensitivity analyses decreased for survival LDCT-screened detected cancers by 1yr.	No	NR	NR	NR
Chirikos 2002[13]	CEA (life-years)	15 years 7.5%	Cohort model. Stage/treatment states: Local – surgery only, Local – other treatment, Regional – single therapies, Regional – multiple therapies, Distant – single therapies, Distant – multiple therapies	Stage shift at diagnosis. SEER	No. By age group and gender categories	No	No	No	NR	NR	NR
Mahadevia 2003[18]	CUA	40 years 3%	Markov model. Unscreened model states: No apparent lung cancer, lung cancer (small cell lung cancer, localised NSCLC or advanced NSCLC), death.	Stage shift at diagnosis. Hypothetical stage shift. SEER.	No. Age & smoking cessation	Allows some LDCT–detected cancers enter a separate (overdiagnosis/length time bias) state in the model	Decreased survival for LDCT-screened detected cancers by an average of 1 year.	Assumes that some cancers progress extremely slow.	No	No	NR

			Screened model states: nonadherent (similar to unscreened model), length or overdiagnosis bias, screened, LC (small cell lung cancer, localised NSCLC or advanced NSCLC), death.								
Wisnivesky 2003[2]	CEA (life-years)	Lifetime 3%	Decision tree model. Usual care probabilities based on SEER. Stages I, II, IIIA, IIIB, IV	(Implicit) stage shift at diagnosis. ELCAP data.	No. Age-specific mortality	In sensitivity analyses, assessed different proportions of screen-detected lung cancers assumed to be overdiagnoses.	1.5 years added to survival of unscreened individuals. Assessed different lead times in sensitivity analyses.	NR	NR	NR	NR
Manser 2005[14]	CUA CEA (life-years)	15 years 3%	Markov model Stages I, II, IIIA, IIIB, IV	Stage shift at diagnosis. Weighted average reported for CT screening studies examining high-risk cohorts.	Yes Accounted for current smoking rates and the relative risk of death from all causes in smokers.	Inflate LDCT screen-detected cancers by **12%** (0% & 20% in sensitivity analyses).	Decreased survival for LDCT-screened detected cancers by an average of 1 year.	NR	NR	No	NR
Whynes 2008[3]	CUA	Assumed life-time 3.5%	Decision tree - Formula for additional costs and survival curves for benefits associated with LDCT screening. Early vs late	Stage shift at diagnosis. ELCAP data.	No Age & gender	NR	Decreased survival for LDCT-screened detected cancers by 8 years (<8 years in sensitivity analyses).	NR	No	No	NR
McMahon 2011[4]	CUA	Lifetime 3%	Lung Cancer Policy Model: patient-level microsimulation model, including lung cancer development, progression, detection, treatment, and survival. Natural history calibration against tumour registry data.	Directly modelled patient-level data. NLST, PLCO and registry data.	Yes estimate cause-specific mortality rates stratified by age, sex, race, and smoking status.	Overdiagnosis is modelled as an output from the natural history and screening processes of the model	Accounting for lead-time bias is inherent within the modelling process and reported as an output.	Accounting for length time bias is inherent within the modelling process and reported	No	Yes, estimate excess relative risks for lung cancer per Gray exposure.	Model has been validated against two screening studies (for rates of positive screens,

			NSCLC stages I, II, IIIa, IIIb, IV SCLC stages LS & ES					as an output.			stage, and cell type distributions) and two cohort studies (for mortality).
Goulart 2012[29]	CEA (lung cancer deaths)	1 year No discount rate	Decision tree model (primarily for budget impact assessment). Applied stage distribution of LDCT-detected lung cancers from NLST to national lung cancer data, then compared this to unadjusted national data. stages I and II as localized, stage III as regional, stage IV as distant.	Stage shift at diagnosis. NLST and national registries.	NA	Inflate LDCT screen-detected cancers by **13%** (0% & 20% in sensitivity analyses).	NR	NR	NR	No	NR
Pyenson 2012[19]	CEA (life-years)	15 years None	Cohort model. Model and compare costs associated with cancer stages (localized, reginal, distant) and survival (by age, gender, and lung cancer stage) for a LDCT screening cohort and a no screening cohort. Stages A, B, C similar to localized, regional, and distant Cancer (from SEER)	Stage-shift at diagnosis. ELCAP data.	No. Age & sex, but included lung cancer survivors	Inflate stage A LDCT screen-detected cancers by 5-20%.	Adjust for this in the stage shift assumption.	NR	NR	NR	NR
Shmueli 2013[5]	CUA	Lifetime 3%	Decision tree model - All negative results are assumed to be true negatives. MECC I: TNM I MECC II:TNM II-III MECC III: TNM IV	Stage shift at diagnosis. Single-centre cohort study (Israel).	No. Life expectancy based on age.	Inflate LDCT screen-detected cancers by 10% (and up to 50% in sensitivity analyses). Used an index k to represent overdiagnosis and self-selection.	Decreased survival for LDCT-screened detected cancers by 2 years (0 & 4yrs in sensitivity analyses).	NR	NR	NR	NR

Villanti 2013[23]	CUA	15 yeas No discount rate reported.	Cohort model (as in Pyenson 2012). A: IA and IB B: IIA, IIB, and IIIA C: IIIB and IV (corresponding to SEER s localized, regional, distant categories)	Stage shift at diagnosis. ELCAP data, NLST.	Yes. mortality rates by smoking history	NR	Decreased survival for LDCT-screened detected cancers by 2 years (0 & 4yrs in sensitivity analyses).	NR	NR	No	NR
Black 2014[10]	CUA CEA (life-years)	Lifetime 3%	Decision tree model NLST stage-specific mortality: IA, IB, II, III, IV	Direct modelling of data NLST and SEER	Yes. Age, sex, smoking status.	Accounted for additional lung cancers in screened arm to be overdiagnosis	NR	NR	Included costs of dealing with incidental findings for a proportion of LDCT screening population	Included costs of future cancers due to radiation exposure	Looked at internal consistency of their analysis
Pyenson 2014[20]	CEA (life-years)	20 years None	Cohort model (as used in Pyenson 2012). Modelled stages A-C: A: IA, IB B: IIA, IIB, IIIA C: IIIB, IV	Stage shift at diagnosis. NLST, ELCAP data, SEER.	Yes Report reducing mortality rate "appropriate for smokers."	In sensitivity analyses inflate stage A LDCT screen-detected cancers by 20%.	Only calculated life-years saved due to the impact of the stage shift.	NR	NR	NR	NR
Tabata 2014[30]	CEA (life-years)	Lifetime Discount rate not reported	Decision tree model, based on national datasets and screening study. Early vs late stage	Stage shift at diagnosis. Case-control study (Japan).	Unclear, but looks like only age & gender	Inflate LDCT-detected cancers by minimum of 0% and maximum of 30%.	NR	NR, but "addressed to some extent with assumptions for overdiagnosis".	NR	NR	NR
Goffin 2015[9]	CUA	20 years 3%	Cancer Risk Management Model – Lung Cancer module. This is a microsimulation model, including a natural history model calibrated to NLST. Stage I, II, III, IV	Stage shift at diagnosis. NLST.	Unclear	Inflate LDCT screen-detected lung cancers by 18% over 3 annual screens (10% at first screen, 4% at second and third screens).	Yes, though details unclear.	Yes, though details unclear.	NR	No	Internal validity, and model compared with other work (authors report "encouraging" results)

Field 2015[7]	CUA CEA (life-years)	Lifetime 3.5%	Decision tree - Formula for additional costs and survival curves for benefits Stage I, II, III, IV	Stage shift at diagnosis. UKLS pilot.	No. Mortality by age	Adjustments for lead-time bias also account for overdiagnosis.	Decreased survival for LDCT-screened detected cancers depending on stage at diagnosis: 6 years for stage 1, 4 years for stage 2, 2 years for stage 3.	NR	No	NR	NR
Goffin 2016[31]	CUA	Life-time 3%	Oncosim – formerly the Cancer Risk Management Model. This is a microsimulation model, including a natural history model calibrated to NLST. Assume model Stage I, II, III, IV as Goffin 2015	Stage shift at diagnosis. NLST and Canadian cancer registry data.	Unclear	NR. Assumed as in Goffin 2015.	Yes, adjust preclinical duration in the screening arm by stage.	NR.	NR	NR	Compared modelled cancer incidence and mortality with cancer registry data (but use cancer registry data in model). Internal validation reported, and good face validity.
Cressman 2017[11]	CUA	30 years 3%	Three Markov models: 1. High-risk screened 2. High-risk unscreened 3. Low-risk unscreened Intervention arm = Models 1+2+3 Control arm = Models 2+3. States: screening, curative treatment, noncurative treatment, progression, death.	Stage shift at diagnosis. Modelled by whether transition to curative (IA to IIIA) or non-curative (IIIB to IV) health state. NLST.	No	In a scenario analysis assumed higher post screening lung cancer rates (by increasing the transition probabilities for noncurative treatment by 10%).	NR – unclear if captured in the modelling approach	NR – unclear if captured in the modelling approach	Included costs of dealing with "actionable" incidental findings.	No	NR
ten Haaf 2017[21]	CEA (life-years)	Lifetime 3%	MISCAN-Lung is a semi-Markov stochastic model simulating individuals from birth until death.	Stage shift at diagnosis.	Yes Age, gender and smoking behaviour	Overdiagnosis is modelled as an output from the natural history and screening	Accounting for lead-time bias is inherent within the	Accounting for length time bias is inherent	Include costs for " Non-lung cancer	NR	Compared modelled proportions of histological

			It involves modules for individual characteristics (including smoking history), association of smoking exposure to lung carcinogenesis, natural history of lung cancer disease (calibrated to RCT data) and a module to capture the impacts of screening. The probability of developing preclinical lung cancer and dying from other causes, depends on smoking exposure. Lung cancer progresses through stages IA, IB, II, IIIA, IIIB to IV.	NLST and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.		processes of the model	modelling process and reported as an output	within the modelling process and reported as an output	surgery for potentially benign disease"		types, clinical stages, and lung cancer incidence with observed data.
Treskova 2017[16]	CEA (life-years, averted lung cancer deaths)	Lifetime 3%	Stochastic microsimulation model including modules on population, natural history (using equations from a previous model), clinical detection, survival, screening and life history. Stages I, II, III, IV	Reduced mortality associated with LDCT screen-detected stage I and II cancers. Multiple sources including NLST.	Yes Age, gender and whether never-, current- or former smoker	Overdiagnosis is modelled as an output from the natural history and screening processes of the model	Accounting for lead-time bias is inherent within the modelling process	Accounting for length time bias is inherent within the modelling process	NR	Includes deaths from radiation-induced cancers.	Report validation against NLST outputs.
Yang 2017[32]	CUA	Lifetime 3%	Decision tree model Stages I, II, IIIA, IIIB, IV	Stage shift at diagnosis. NLST.	No. Age and sex. Acknowledge in discussion that smokers all-cause mortality likely to be higher, so benefits of CT could be overestimated	No	Decreased survival for LDCT-screened detected cancers depending on age and stage at diagnosis.	NR	NR	Include costs of, and deaths from,radiation-induced lung cancers	Compared extrapolated survival with observed data
Hinde 2018[6]	CUA	Lifetime 3.5%	Decision tree model - Formula for additional costs and survival curves for benefits	Stage shift at diagnosis.	To some extent. Used local mortality rates to reflect	NR	Decreased survival for LDCT-screened detected	NR	NR	NR	NR

			Stages I, II, III, IV	UK Manchester pilot.	deprivation in that area.		cancers depending on stage at diagnosis: 6 years for stage 1, 4 years for stage 2, 2 years for stage 3.				
Hofer 2018[27]	CUA, CEA (life-years)	15 years 3%	Two cohort Markov models: a natural history model and a treatment and aftercare model Stages I, II, IIIA, IIIB, IV	Stage shift at diagnosis. NELSON, ITALUNG, LUSI, ten Haaf[ref]	Yes. Adjusted for former and current heavy smokers	No	NR	NR	NR	No	NR
Kumar 2018[33]	CUA CEA (life-years)	Lifetime 3%	Multistate model, with a continuous-time framework, so uses individual patient-level data. Estimates several transitions simultaneously, so deals with semicompeting risks for the diagnosis of lung cancer and death. Does not account for cancer stage.	Directly modelled individual-participant data. NLST.	Use NLST data	Allowed individuals in LDCT arm to transition more quickly to lung cancer diagnosis than those in control arm, but transition to lung cancer death was modelled to be slower.	NR – unclear if captured in the modelling approach	Adjustment for overdiagnosis accounts for this.	No	NR	Used calibration plots for observed events versus predicted risks, and used c-statistic for model discrimination.
Snowsill 2018[8]	CUA	Lifetime 3.5%	DES model informed by a natural history model (calibrated to NLST). Stages IA, IB, IIA, IIB, IIIA, IIIB, IV	Stage shift at diagnosis. NLST.	Yes	Overdiagnosis is modelled as an output from the natural history and screening processes of the model.	Accounting for lead-time bias is inherent within the modelling process and reported as an output	Accounting for length time bias is inherent within the modelling process	No	No	Face validity assessed by patient and public group. Quality assurance of model reported.
Tomonaga 2018[22]	CEA (lung cancer incidence, lung cancer mortality, life-years)	Lifetime 3%	MISCAN-Lung (as in ten Haaf). Natural history model calibrated to RCT data. Lung cancer progresses through stages IA, IB, II, IIIA, IIIB to IV.	Stage shift at diagnosis. NLST and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.	Yes Gender and smoking behaviour	Overdiagnosis is modelled as an output from the natural history and screening processes of the model.	Accounting for lead-time bias is inherent within the modelling process and reported as an output	Accounting for length time bias is inherent within the modelling process and reported	NR	NR	Compared modelled lung cancer incidence, histology proportions and stage proportions to observed data

								as an output			
Wade 2018[12]	CUA CEA (Life-years)	10 years 5%	Decision tree – Re-analysis of individual-participant data extrapolating with Australian lifetables. NSCLC: I, II, III, IV SCLC: Limited, extensive	Re-analysis of individual participant data. NLST, local registry data.	Yes Adjusted for smoking status	No	NR	No	In sensitivity analyses assume costs of dealing with incidental findings.	No	NR
Criss 2019[24]	CUA, CEA (life-years)	45 years 3%	4 LC models: 1. MISCAN-Lung 2. Lung Cancer Policy Model 3. University of Michigan Lung Cancer Screening model 4. Lung Cancer Outcomes Simulator	See individual models	See individual models	See individual models	See individual models	See individual models	See individual models	See individual models	Reproduced observed lung cancer incidence and mortality data from U.S. studies
Toumazis 2019[26]	CUA	Lifetime 3%	Lung Cancer Outcomes Simulator. Natural history model estimated by maximum likelihood based on SEER data. Early NSCSLC vs SCLC or advanced NSCLC	Stage shift at diagnosis	Yes.	Overdiagnosis is modelled as an output from the natural history and screening processes of the model	Accounting for lead-time bias is inherent within the modelling process	NR – unclear if inherent within the modelling process	No	NR	Reproduced observed sex-specific lung cancer US mortality and incidence rates.
Allen 2020[34]	CEA (life-years)	Lifetime No discount rate reported	Markov cohort model: alive no cancer, alive cancer (subdivided into alive with pre-clinical cancer and alive with clinically detectable cancer), dead. Uses MISCAN-Lung Stage IA, IB, II, IIIA, IIIB, IV	Stage-shift at diagnosis NLST	Yes. Gender and smoking behaviour	NR – unclear if inherent within the modelling process	NR – unclear if inherent within the modelling process	NR – unclear if inherent within the modelling process	NR	NR	Compared diagnostic outcomes with NLST. Found similar false negatives, false positives, true negatives and true positives.
Du 2020[25]	CEA (life-years)	Lifetime 4% for costs; 1.5% for	Adapted the "microsimulation model Simulation Model on Radiation	Stage-shift at diagnosis.	Yes Age in heavy smokers	NR – unclear if inherent within the modelling process	NR – unclear if inherent within the modelling process	NR – unclear if inherent within the	NR	Yes. Number of radiation-induced tumours is	Compared simulated outcomes with

		health effects	Risk and cancer Screening (SiMRiSc)" Costs: Stage I – III Stages IV Disease progression: TNM stage at diagnosis (diameter a proxy for T stage)	Sensitivity of LDCT is a function of tumour size.				modelling process		a model output. Costs and health effects of these included in model.	the observed data from NELSON
Guzman 2020[36]	CBA (assuming €30,000 per LYG)	Up to 10 years 3%	Decision tree approach. Surgical vs medically treated cancers	Assumes screening arm identified more cases. Survival based on local data and literature. NLST	Yes. Mortality from local lung cancer patients.	No	No	No	No	NR	No
Jaine 2020[28]	CUA	Lifetime 3%	Markov model. States: healthy, SEER local stage lung cancer, SEER regional stage lung cancer, SEER distant stage lung cancer, death from lung cancer, death other.	Stage shift at diagnosis. NLST and NZ data	Yes. The Statistics New Zealand life tables provided us with overall mortality by age, which we have previously disaggregated by smoking status (i.e. never smoker, ex-smoker and current smoker) to calculate relative risks [29]. However, given that mortality (i.e. non-lung cancer deaths as well) will be higher in the 30+ pack year population, all-cause mortality was scaled up **using estimates of the risk of death by smoking intensity** (see Methods	Inflate LDCT screen-detected cancers by 11%.	Decreased survival for LDCT-screened detected cancers by 6 months (0 & 1 year in sensitivity analyses)	NR	Include costs for dealing with incidental findings	NR	NR

					Appendix in Supplementary material for further detail).						
Veronesi[17]	CUA, CEA (life-years)	5 years 3%	Decision tree model Stages IA, IB, II, III, IV	Stage shift at diagnosis. COSMOS study & local data.	Unclear. Mention obtain data from those "at high risk of lung cancer"	NR	Adjusted for 2-year lead-time. In sensitivity analyses looked at 0 and 3 years for stages 3 and 4, 0 and 6 years for stages 1 and 2.	NR	No	NR	NR

Appendix 6. Summary of critical appraisal (sorted by year of publication)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Marshall[15]*	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	U	Y	Y	N	Y	Y	N	N
Marshall[1]*	N	Y	N	N	N	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	N	N	N
Chirikos[13]*	N	Y	N	N	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	N	N	N
Mahadevia[18]*	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	N
Wisnivesky[2]*	Y	Y	Y	N	U	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	N	N
Manser[14]*	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	N	U	N
Whynes[3]*	Y	Y	Y	N	U	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	U	N
McMahon[4]*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	U	N
Goulart[29]*	Y	N	N	N	N	Y	Y	Y	N	N	Y	N	Y	N	N	Y	N	Y	N
Pyenson[19]*	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	U	N	P**	N
Shmueli[5]*	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	U	N
Villanti[23]*	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N
Black[10]*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N
Pyenson[20]*	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	N	N	N
Tabata[30]*	Y	Y	Y	N	U	U	U	U	U	N	Y	Y	Y	U	N	Y	N	N	N
Goffin[9]*	Y	Y	Y	Y	Y	Y	U	U	U	Y	Y	U	N	Y	N	Y	Y	N	N
Field[7]*	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	N	Y	Y	N	N
Goffin[31]*	Y	Y	Y	Y	Y	U	U	U	U	Y	Y	U	N	Y	N	Y	N	N	N
Cressman 2017[11]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	U
ten Haaf[21]*	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	P**	N
Treskova 2017[16]	Y	Y	Y	U	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	P**	U
Yang 2017[32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	U
Hinde 2018[6]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	N	Y	Y	Y	U
Hofer 2018[27]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y
Kumar 2018[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	N	Y	Y	P**	N
Snowsill 2018[8]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N
Tomonaga 2018[22]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	U	Y	Y	N	U	U	N	N
Wade 2018[12]	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P**	U
Criss 2019[24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	N	P**	N
Toumazis 2019[26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Allen 2020[34]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	U	Y	U	N	Y	Y	Y	N
Du 2020[25]	Y	Y	Y	U	Y	Y	Y	U	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N
Guzman 2020[36]	Y	N	Y	Y	U	Y	U	U	Y	N	Y	U	Y	U	N	Y	N	Y	N
Jaine 2020[28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	U
Veronesi 2020[17]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	P**	N

* Taken from Snowsill 2018[8]

**Partial indication: e.g. ten Haaf declare funders had no role in the study, but report potential conflicts of interest for some authors

1. Is the study population clearly described?
2. Are competing alternatives clearly described?
3. Is a well-defined research question posed in answerable form?
4. Is the economic study design appropriate to the stated objective? (i.e. was the economic evaluation principally based on a RCT of lung cancer screening without significant unsupported assumptions?)
5. Is the chosen time horizon appropriate to include relevant costs and consequences?
6. Is the actual perspective chosen appropriate?
7. Are all important and relevant costs for each alternative identified? (all of the following were required: screening scan costs, costs of follow-up tests for all positive or indeterminate screening scans, costs of diagnosing, staging and treating lung cancer)
8. Are all resources measured appropriately in physical units?
9. Are resources valued appropriately?
10. Are all important and relevant outcomes for each alternative identified? (all of the following were required: lung cancer diagnoses, lung cancer deaths, life-years, QALYs)
11. Are all outcomes measured appropriately in physical units?
12. Are outcomes valued appropriately?
13. Is an incremental analysis of costs and outcomes performed?
14. Are all future costs and outcomes discounted appropriately?
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?
16. Do the conclusions follow from the data reported?
17. Does the study discuss the generalisability of the results to other settings and patient/client groups?
18. Does the article indicate that there is not potential conflict of interest of study researcher(s) and funder(s)?
19. Are ethical and distributional issues discussed appropriately?

References

1. Marshall D, Simpson KN, Earle CC, Chu C. Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort. *Lung Cancer.* 2001;32(3):227-236.
2. Wisnivesky JP, Mushlin AI, Sicherman N, Henschke C. The cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. *Chest.* 2003;124(2):614-621.
3. Whynes DK. Could CT screening for lung cancer ever be cost effective in the United Kingdom? *Cost effectiveness and resource allocation : C/E.* 2008;6:5.
4. McMahon PM, Kong CY, Bouzan C, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. *J Thorac Oncol.* 2011;6(11):1841-1848.
5. Shmueli A, Fraifeld S, Peretz T, et al. Cost-effectiveness of baseline low-dose computed tomography screening for lung cancer: the Israeli experience. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2013;16(6):922-931.
6. Hinde S, Crilly T, Balata H, et al. The cost-effectiveness of the Manchester 'lung health checks', a community-based lung cancer low-dose CT screening pilot. *Lung Cancer.* 2018;126:119-124.
7. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health technology assessment (Winchester, England).* 2016;20(40):1-146.
8. Snowsill T, Yang H, Griffin E, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. *Health Technol Assess.* 2018;22(69):1-276.
9. Goffin JR, Flanagan WM, Miller AB, et al. Cost-effectiveness of Lung Cancer Screening in Canada. *JAMA oncology.* 2015;1(6):807-813.
10. Black WC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. *The New England journal of medicine.* 2014;371(19):1793-1802.
11. Cressman S, Peacock SJ, Tammemagi MC, et al. The Cost-Effectiveness of High-Risk Lung Cancer Screening and Drivers of Program Efficiency. *Journal of Thoracic Oncology.* 2017;12(8):1210-1222.
12. Wade S, Weber M, Caruana M, et al. Estimating the Cost-Effectiveness of Lung Cancer Screening with Low-Dose Computed Tomography for High-Risk Smokers in Australia. *J Thorac Oncol.* 2018;13(8):1094-1105.
13. Chirikos TN, Hazelton T, Tockman M, Clark R. Screening for lung cancer with CT: a preliminary cost-effectiveness analysis. *Chest.* 2002;121(5):1507-1514.
14. Manser R, Dalton A, Carter R, Byrnes G, Elwood M, Campbell DA. Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting. *Lung Cancer.* 2005;48(2):171-185.
15. Marshall D, Simpson KN, Earle CC, Chu CW. Economic decision analysis model of screening for lung cancer. *Eur J Cancer.* 2001;37(14):1759-1767.
16. Treskova M, Aumann I, Golpon H, Vogel-Claussen J, Welte T, Kuhlmann A. Trade-off between benefits, harms and economic efficiency of low-dose CT lung cancer screening: a microsimulation analysis of nodule management strategies in a population-based setting. *BMC Med.* 2017;15(1):162.
17. Veronesi G, Navone N, Novellis P, et al. Favorable incremental cost-effectiveness ratio for lung cancer screening in Italy. *Lung Cancer.* 2020;143:73-79.
18. Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *Jama.* 2003;289(3):313-322.

19. Pyenson BS, Sander MS, Jiang Y, Kahn H, Mulshine JL. An actuarial analysis shows that offering lung cancer screening as an insurance benefit would save lives at relatively low cost. *Health affairs (Project Hope).* 2012;31(4):770-779.
20. Pyenson BS, Henschke CI, Yankelevitz DF, Yip R, Dec E. Offering lung cancer screening to high-risk medicare beneficiaries saves lives and is cost-effective: an actuarial analysis. *American health & drug benefits.* 2014;7(5):272-282.
21. Ten Haaf K, Tammemägi MC, Bondy SJ, et al. Performance and Cost-Effectiveness of Computed Tomography Lung Cancer Screening Scenarios in a Population-Based Setting: A Microsimulation Modeling Analysis in Ontario, Canada. *PLoS medicine.* 2017;14(2):e1002225.
22. Tomonaga Y, Ten Haaf K, Frauenfelder T, et al. Cost-effectiveness of low-dose CT screening for lung cancer in a European country with high prevalence of smoking-A modelling study. *Lung Cancer.* 2018;121:61-69.
23. Villanti AC, Jiang Y, Abrams DB, Pyenson BS. A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. *PloS one.* 2013;8(8):e71379.
24. Criss SD, Cao P, Bastani M, et al. Cost-Effectiveness Analysis of Lung Cancer Screening in the United States: A Comparative Modeling Study. *Ann Intern Med.* 2019;171(11):796-804.
25. Du Y, Sidorenkov G, Heuvelmans MA, et al. Cost-effectiveness of lung cancer screening with low-dose computed tomography in heavy smokers: a microsimulation modelling study. *Eur J Cancer.* 2020;135:121-129.
26. Toumazis I, Tsai EB, Erdogan SA, et al. Cost-Effectiveness Analysis of Lung Cancer Screening Accounting for the Effect of Indeterminate Findings. *JNCI cancer spectr.* 2019;3(3):pkz035.
27. Hofer F, Kauczor HU, Stargardt T. Cost-utility analysis of a potential lung cancer screening program for a high-risk population in Germany: A modelling approach. *Lung Cancer.* 2018;124:189-198.
28. Jaine R, Kvizhinadze G, Nair N, Blakely T. Cost-effectiveness of a low-dose computed tomography screening programme for lung cancer in New Zealand. *Lung Cancer.* 2020;144:99-106.
29. Goulart BH, Bensink ME, Mummy DG, Ramsey SD. Lung cancer screening with low-dose computed tomography: costs, national expenditures, and cost-effectiveness. *Journal of the National Comprehensive Cancer Network : JNCCN.* 2012;10(2):267-275.
30. Tabata H, Akita T, Matsuura A, et al. Cost-effectiveness of the introduction of low-dose CT screening in Japanese smokers aged 55 to 74 years old. *Hiroshima journal of medical sciences.* 2014;63(1-3):13-22.
31. Goffin JR, Flanagan WM, Miller AB, et al. Biennial lung cancer screening in Canada with smoking cessation-outcomes and cost-effectiveness. *Lung Cancer.* 2016;101:98-103.
32. Yang SC, Lai WW, Lin CC, et al. Cost-effectiveness of implementing computed tomography screening for lung cancer in Taiwan. *Lung Cancer.* 2017;108:183-191.
33. Kumar V, Cohen JT, van Klaveren D, et al. Risk-Targeted Lung Cancer Screening: A Cost-Effectiveness Analysis. *Ann Intern Med.* 2018;168(3):161-169.
34. Allen BD, Schiebler ML, Sommer G, et al. Cost-effectiveness of lung MRI in lung cancer screening. *Eur Radiol.* 2020;30(3):1738-1746.
35. Du Y, Sidorenkov G, Heuvelmans MA, et al. Supplementary data for a model-based health economic evaluation on lung cancer screening with low-dose computed tomography in a high-risk population. *Data Brief.* 2020;31:105999.
36. Guzman R, Guirao À, Vela E, et al. Outcomes and cost of lung cancer patients treated surgically or medically in Catalunya: cost-benefit implications for lung cancer screening programs. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP).* 2020.