SaxInstitute

Evidence Check

Lung cancer screening using low-dose computed tomography for high risk populations

An Evidence Check rapid review brokered by the Sax Institute for the Cancer Institute—October 2019

An **Evidence Check** rapid review brokered by the Sax Institute for the Cancer Institute NSW.
October 2019

This report was prepared by:

Nicole Rankin, Deborah McGregor, Candice Donnelly, Bethany Van Dort, Richard De Abreu Lourenco, Anne Cust, and Emily Stone.

doi:10.57022/clzt5093

October 2019
© Cancer Institute NSW 2019

This work is copyright. It may be reproduced in whole or in part for study training purposes subject to the inclusions of an acknowledgement of the source. It may not be reproduced for commercial usage or sale. Reproduction for purposes other than those indicated above requires written permission from the copyright owners.

Enquiries regarding this report may be directed to the:

Manager
Knowledge Exchange Program
The Sax Institute
www.saxinstitute.org.au
knowledge.exchange@saxinstitute.org.au
Phone: +61 2 9188 9500

Suggested Citation:

Rankin N, McGregor D, Donnelly C, Van Dort B, De Abreu Lourenco R, Cust A, Stone E. Lung cancer screening using low-dose computed tomography for high risk populations: Investigating effectiveness and screening program implementation considerations: An Evidence Check rapid review brokered by the Sax Institute (www.saxinstitute.org.au) for the Cancer Institute NSW 2019. doi:10.57022/clzt5093

Disclaimer:

This **Evidence Check Review** was produced using the Evidence Check methodology in response to specific questions from the commissioning agency.

It is not necessarily a comprehensive review of all literature relating to the topic area. It was current at the time of production (but not necessarily at the time of publication). It is reproduced for general information and third parties rely upon it at their own risk.

Lung cancer screening using low-dose computed tomography for high risk populations: Investigating effectiveness and screening program implementation considerations

An **Evidence Check** rapid review brokered by the Sax Institute for the Cancer Institute NSW.
October 2019
This report was prepared by Nicole Rankin, Deborah McGregor, Candice Donnelly, Bethany Van Dort, Richard De Abreu Lourenco, Anne Cust and Emily Stone.

Contents

Executive summary

Background

Lung cancer is the number one cause of cancer death worldwide.[1] It is the fifth most commonly diagnosed cancer in Australia (12,741 cases diagnosed in 2018) and the leading cause of cancer death.[2] The number of years of potential life lost to lung cancer in Australia is estimated to be 58,450, similar to that of colorectal and breast cancer combined.(3) While tobacco control strategies are most effective for disease prevention in the general population, early detection via low dose computed tomography (LDCT) screening in high-risk populations is a viable option for detecting asymptomatic disease in current (13%) and former (24%) Australian smokers.(4)

The purpose of this Evidence Check review is to identify and analyse existing and emerging evidence for LDCT lung cancer screening in high-risk individuals to guide future program and policy planning.

Evidence Check questions

This review aimed to address the following questions:

1. What is the evidence for the effectiveness of lung cancer screening for higher-risk individuals?
2. What is the evidence of potential harms from lung cancer screening for higher-risk individuals?
3. What are the main components of recent major lung cancer screening programs or trials?
4. What is the cost-effectiveness of lung cancer screening programs (include studies of cost–utility)?

Summary of methods

The authors searched the peer-reviewed literature across three databases (MEDLINE, PsycINFO and Embase) for existing systematic reviews and original studies published between 1 January 2009 and 8 August 2019. Fifteen systematic reviews (of which 8 were contemporary) and 64 original publications met the inclusion criteria set across the four questions.

Key findings

Question 1: What is the evidence for the effectiveness of lung cancer screening for higher-risk individuals?

There is sufficient evidence from systematic reviews and meta-analyses of combined (pooled) data from screening trials (of high-risk individuals) to indicate that LDCT examination is clinically effective in reducing lung cancer mortality. In 2011, the landmark National Lung Cancer Screening Trial (NLST, a large-scale randomised controlled trial [RCT] conducted in the US) reported a 20% (95% CI 6.8% – 26.7%; P=0.004) relative reduction in mortality among long-term heavy smokers over three rounds of annual screening. High-risk eligibility criteria was defined as people aged 55–74 years with a smoking history of ≥30 pack-years (years in which a smoker has consumed 20-plus cigarettes each day) and, for former smokers, ≥30 pack-years and have quit within the past 15 years.(5) All-cause mortality was reduced by 6.7% (95% CI, 1.2% – 13.6%; P=0.02). Initial data from the second landmark RCT, the NEderlands-Leuvens Longkanker Screenings ONderzoek (known as the NELSON trial), have found an even greater reduction of 26% (95% CI, 9% – 41%) in lung cancer mortality, with full trial results yet to be published.(6, 7) Pooled analyses, including several smaller-scale European LDCT screening trials insufficiently powered in their own right, collectively demonstrate a statistically significant reduction in lung cancer mortality (RR 0.82, 95% CI 0.73–0.91).(8)

Despite the reduction in all-cause mortality found in the NLST, pooled analyses of seven trials found no statistically significant difference in all-cause mortality (RR 0.95, 95% CI 0.90–1.00).(8) However, cancer-specific mortality is currently the most relevant outcome in cancer screening trials. These seven trials demonstrated a significantly greater proportion of early stage cancers in LDCT groups compared with controls (RR 2.08, 95% CI 1.43–3.03). Thus, when considering results across mortality outcomes and early stage cancers diagnosed, LDCT screening is considered to be clinically effective.

Question 2: What is the evidence of potential harms from lung cancer screening for higher-risk individuals?

The harms of LDCT lung cancer screening include false positive tests and the consequences of unnecessary invasive follow-up procedures for conditions that are eventually diagnosed as benign. While LDCT screening leads to an increased frequency of invasive procedures, it does not result in greater mortality soon after an invasive procedure (in trial settings when compared with the control arm).(8) Overdiagnosis, exposure to radiation, psychological distress and an impact on quality of life are other known harms. Systematic review evidence indicates the benefits of LDCT screening are likely to outweigh the harms.

The potential harms are likely to be reduced as refinements are made to LDCT screening protocols through: i) the application of risk predication models (e.g. the $PLCO_{m2012}$), which enable a more accurate selection of the high-risk population through the use of specific criteria (beyond age and smoking history); ii) the use of nodule management algorithms (e.g. Lung-RADS, PanCan), which assist in the diagnostic evaluation of screen-detected nodules and cancers (e.g. more precise volumetric assessment of nodules); and, iii) more judicious selection of patients for invasive procedures.

Recent evidence suggests a positive LDCT result may transiently increase psychological distress but does not have long-term adverse effects on psychological distress or health-related quality of life (HRQoL). With regards to smoking cessation, there is no evidence to suggest screening participation invokes a false sense of assurance in smokers, nor a reduction in motivation to quit. The NELSON and Danish trials found no difference in smoking cessation rates between LDCT screening and control groups. Higher net cessation rates, compared with general population, suggest those who participate in screening trials may already be motivated to quit.

Question 3: What are the main components of recent major lung cancer screening programs or trials?

There are no systematic reviews that capture the main components of recent major lung cancer screening trials and programs. We extracted evidence from original studies and clinical guidance documents and organised this into key groups to form a concise set of components for potential implementation of a national lung cancer screening program in Australia:

1. Identifying the high-risk population: recruitment, eligibility, selection and referral
2. Educating the public, people at high risk and healthcare providers; this includes creating awareness of lung cancer, the benefits and harms of LDCT screening, and shared decision-making
3. Components necessary for health services to deliver a screening program:
    a. Planning phase: e.g. human resources to coordinate the program, electronic data systems that integrate medical records information and link to an established national registry
    b. Implementation phase: e.g. human and technological resources required to conduct LDCT examinations, interpretation of reports and communication of results to participants
    c. Monitoring and evaluation phase: e.g. monitoring outcomes across patients, radiological reporting, compliance with established standards and a quality assurance program
4. Data reporting and research, e.g. audit and feedback to multidisciplinary teams, reporting outcomes to enhance international research into LDCT screening

5. Incorporation of smoking cessation interventions, e.g. specific programs designed for LDCT screening or referral to existing community or hospital-based services that deliver cessation interventions.

Most original studies are single-institution evaluations that contain descriptive data about the processes required to establish and implement a high-risk population-based screening program. Across all studies there is a consistent message as to the challenges and complexities of establishing LDCT screening programs to attract people at high risk who will receive the greatest benefits from participation.

With regards to smoking cessation, evidence from one systematic review indicates the optimal strategy for incorporating smoking cessation interventions into a LDCT screening program is unclear. There is widespread agreement that LDCT screening attendance presents a 'teachable moment' for cessation advice, especially among those people who receive a positive scan result. Smoking cessation is an area of significant research investment; for instance, eight US-based clinical trials are now underway that aim to address how best to design and deliver cessation programs within large-scale LDCT screening programs.(9)

Question 4: What is the cost-effectiveness of lung cancer screening programs (include studies of cost–utility)?

Assessing the value or cost-effectiveness of LDCT screening involves a complex interplay of factors including data on effectiveness and costs, and institutional context. A key input is data about the effectiveness of potential and current screening programs with respect to case detection, and the likely outcomes of treating those cases sooner (in the presence of LDCT screening) as opposed to later (in the absence of LDCT screening).

Evidence about the cost-effectiveness of LDCT screening programs has been summarised in two systematic reviews. We identified a further 13 studies—five modelling studies, one discrete choice experiment and seven articles—that used a variety of methods to assess cost-effectiveness. Three modelling studies indicated LDCT screening was cost-effective in the settings of the US and Europe. Two studies—one from Australia and one from New Zealand—reported LDCT screening would not be cost-effective using NLST-like protocols. We anticipate that, following the full publication of the NELSON trial, cost-effectiveness studies will likely be updated with new data that reduce uncertainty about factors that influence modelling outcomes, including the findings of indeterminate nodules.

Gaps in the evidence

There is a large and accessible body of evidence as to the effectiveness (Q1) and harms (Q2) of LDCT screening for lung cancer. Nevertheless, there are significant gaps in the evidence about the program components that are required to implement an effective LDCT screening program (Q3). Questions about LDCT screening acceptability and feasibility were not explicitly included in the scope. However, as the evidence is based primarily on US programs and UK pilot studies, the relevance to the local setting requires careful consideration. The Queensland Lung Cancer Screening Study provides feasibility data about clinical aspects of LDCT screening but little about program design. The International Lung Screening Trial is still in the recruitment phase and findings are not yet available for inclusion in this Evidence Check.

The Australian Population Based Screening Framework was developed to *"inform decision-makers on the key issues to be considered when assessing potential screening programs in Australia"*.(10) As the Framework is specific to population-based, rather than high-risk, screening programs, there is a lack of clarity about transferability of criteria. However, the Framework criteria do stipulate that a screening program must be acceptable to *"important subgroups such as target participants who are from culturally and linguistically diverse backgrounds, Aboriginal and Torres Strait Islander people, people from disadvantaged groups and people with a disability"*.(10) An extensive search of the literature highlighted that there is very little

information about the acceptability of LDCT screening to these population groups in Australia. Yet they are part of the high-risk population.(10)

There are also considerable gaps in the evidence about the cost-effectiveness of LDCT screening in different settings, including Australia. The evidence base in this area is rapidly evolving and is likely to include new data from the NELSON trial and incorporate data about the costs of targeted- and immuno-therapies as these treatments become more widely available in Australia.

Discussion of key findings

Question 1: What is the evidence for the effectiveness of lung cancer screening for higher-risk individuals?

There is sufficient evidence as to the clinical effectiveness of LDCT to meet the Population Base Screening Framework criteria for a suitable test. The overall quality of international trials is high (based on systematic review). Further large-scale RCTs are unlikely to be initiated beyond a current RCT in China.(11) Clinical effectiveness data from pooled analysis of trials, including NELSON, will inform the future evidence base.

Question 2: What is the evidence of potential harms from lung cancer screening for higher risk-individuals?

The evidence for LDCT screening suggests the harms of LDCT screening (false positives, overdiagnosis, morbidity and mortality from invasive procedures, radiation exposure) are being minimised through continual improvements in protocols for issues including (but not limited to) nodule management and participant selection. The Population Base Screening Framework criteria state that a screening program *"should give more benefit than harm to the target population"*.(10) The evidence suggests the benefits now outweigh the harms.

Question 3: What are the main components of recent major lung cancer screening programs or trials?

The evidence about the program components of LDCT screening is sourced from large-scale trials, original studies and policy guidance. There is a significant paucity of Australian data that enables the program components to be determined outside the trial setting. These gaps need to be addressed in the short term prior to policy change to recommend a national LDCT screening program.

Question 4: What is the cost-effectiveness of lung cancer screening programs?

While international evidence about cost-effectiveness is not equivocal, evidence is rapidly emerging to show LDCT screening can be cost-effective in some settings. More Australian data are needed on this topic.

Applicability of the findings for NSW

Overall, the findings of this Evidence Check are applicable to the NSW setting, particularly with regards to effectiveness (Q1), harms (Q2) and cost-effectiveness (Q4). Further work is required to establish the applicability of program components (Q3). A review of policy documents was out of scope; however, an analysis of how LDCT programs operate across a mixed model of public–private provision of healthcare services would benefit an understanding of how a national screening program would be designed and implemented to meet the needs of high-risk populations.

Conclusion

The Evidence Check identified that LDCT screening is clinically effective and appears to have greater benefits in reducing mortality than harms. The evidence base concerning LDCT screening is rapidly changing and will further evolve following the full publication of the NELSON trial results. Results from the ILST cohort trial in Australia, Canada and Hong Kong will provide further evidence about effectiveness and cost-effectiveness relevant to NSW. However, a significant investment in real-world implementation is required to understand

how program components could be effectively implemented in a high-risk population in the Australian setting.

Background

The Cancer Institute NSW (the Institute) is a NSW government agency charged with substantially improving cancer control through the NSW Cancer Plan. The goals of the Institute are to:

1. Reduce the incidence of cancer in the community
2. Increase the survival rate for people diagnosed with cancer
3. Improve the quality of life of people diagnosed with cancer and their carers
4. Provide a source of expertise on cancer control for the government, health service providers, medical researchers and the general community.

A major program of the NSW Cancer Plan involves the prevention and early detection of cancer. The Institute's Cancer Screening and Prevention Division is responsible for the delivery of state-wide population-based screening programs for the detection of breast, bowel and cervical cancer. In addition, the division oversees tobacco control, skin and healthy lifestyle cancer prevention, business intelligence, innovation and quality and information systems.

The Cancer Institute NSW has a goal of reducing the use of tobacco and tobacco products and conducts programs, initiatives and campaigns to achieve this goal. Historically, lung cancer programs have focused on primary prevention interventions to reduce tobacco use in the Australian population. Recent studies have investigated the effectiveness of lung cancer screening programs that focus on early detection to reduce mortality from lung cancer.

This Evidence Check was conducted to identify and analyse existing and emerging evidence for lung cancer screening in high-risk individuals and will be used to guide future program and policy planning.

Lung cancer

Lung cancer is the number one cause of cancer death worldwide.(1) It is the fifth most commonly diagnosed cancer in Australia (12,741 cases diagnosed in 2018) and the leading cause of cancer death.(2) Five-year survival is poor (17%) and the majority of people present with incurable disease: 42% of cases are diagnosed at stage IV (the most advanced), while a further 29% of cases are not staged at all (which is attributed mainly to difficulties in obtaining a histological diagnosis).(2) The number of years of potential life lost to lung cancer in Australia is estimated to be 58,450, similar to that of colorectal and breast cancer combined.(3) Lung cancer has the highest cancer burden in the country (18.6% of the total burden).(2) Incidence is expected to continue to rise in Australia and globally.(2, 12) The proportion of lung cancer diagnoses attributed to tobacco use is estimated at about 70%; however, there are significant differences in tobacco use across countries and between women and men.(13) While tobacco control strategies are most effective for disease prevention in the general population, early detection via low dose computed tomography (LDCT) screening in high-risk populations is a viable option for detecting asymptomatic disease in current (13%) and former (24%) Australian smokers.(4)

Lung nodules

A key element of lung cancer screening is the detection of a lung (or pulmonary) nodule and determining whether the nodule is benign (harmless) or is a lung cancer. A nodule is defined as *"a rounded or irregular opacity, which may be well or poorly defined, measuring ⩽3 cm in diameter"*.(14) Larici et al. note that the "determination of lung nodule malignancy is pivotal" to early cancer diagnosis; and while there is "no single method for measuring nodules", size and growth rate represent the main indicators in determining the

nature of a lung nodule.(15) The introduction of computed tomography (CT) has enabled better detection of nodules than through the use of x-ray technology, ensuring that cancers can be detected at a very early stage, but the vast majority of nodules detected are benign.[14] Indeed, 96% of lung nodules in the NLST were not cancer(5, 16), but since that trial more accurate ways have been developed to determine which nodules are harmless and which are cancer. LDCT screening needs to identify those nodules that are cancer and those that are harmless, so people with harmless nodules do not receive additional unnecessary investigations while people with cancer are detected. About one quarter of nodules will result in an undetermined finding (screen positive) and will require active surveillance to track the nodule over time. Hence, throughout this Evidence Check, much of the cited literature refers to the management of lung nodules and advances in techniques to determine malignancy.

Evidence Check purpose

The purpose of this Evidence Check review is to identify and analyse existing and emerging evidence for LDCT lung cancer screening in high-risk individuals to guide future program and policy planning.

Evidence Check questions

This Evidence Check aimed to address the following questions:

1. What is the evidence for the effectiveness of lung cancer screening for higher-risk individuals?
2. What is the evidence of potential harms from lung cancer screening for higher-risk individuals?
3. What are the main components of recent major lung cancer screening programs or trials?
4. What is the cost-effectiveness of lung cancer screening programs (include studies of cost–utility)?

Methods

We developed a PICO statement to guide the literature search (see Appendix 1 for full statement):

- *Population:* High risk (using the NLST criteria as an example): Aged 55–74 years with a smoking history of ≥30 pack-years and, for former smokers, who have quit within the past 15 years
- *Intervention:* Low dose computed tomography (LDCT) screening
- *Comparator:* In the trial setting, no screening test. In non-randomised program evaluations, no comparator
- *(Primary) Outcomes:* Effectiveness, harms, cost-effectiveness and program components.

Peer-reviewed literature

The authors developed a search strategy that was verified by the Cancer Institute NSW. We searched the MEDLINE, PsycINFO and Embase databases on 8 August 2019. The Cochrane Library was also searched for systematic reviews. We identified additional references from searching the reference lists of systematic reviews and expert contribution. The full search strategies are documented in Appendix 2.

Study limitations included publication between 1 January 2009 and 8 August 2019; exceptions were retrieving the protocol or methodology for LDCT trials currently in progress or where analysis is ongoing (for example, the NELSON protocol was published in 2007 and the final trial results are yet to be reported). Studies were limited to full text published in English. The exclusion criteria were:

- Studies focusing on chest X-ray (CXR) and sputum cytology alone (as LDCT is accepted as the gold standard screening test)
- Computer Assisted Diagnostics (CAD) ratings and inter-rater reliability of pulmonary nodules and nodule volumetry
- Technologies delivered in addition to, or in combination with LDCT screening, e.g. magnetic resonance imaging (MRI) and positron emission tomography (PET)
- Blood biomarkers, liquid biopsies, volatile organic compounds, microRNA, radiomic and genomic studies
- Occupational exposures, asbestos and exposures in specific populations such as people with HIV, nuclear industry workers and atomic bomb survivors
- Trial sub-studies investigating other comorbid conditions including (but not limited to) coronary artery disease, chronic obstructive pulmonary disease (COPD) and emphysema.

We removed all duplicates prior to title and abstract screening and used Covidence software(17) to manage the screening of titles and abstracts. We identified a list of potential titles for full-text review and noted reasons for exclusion. One author (DM) reviewed the full texts, with a 20% quality review conducted by a second reviewer (NR or CD). The authors achieved move than 90% concordance and any discrepancies were resolved through discussion or with a third reviewer (CD, NR or BVD). Articles included for full-text review were exported from Covidence into Endnote software.(18)

Included studies and data extraction

The literature search identified 1559 potentially relevant articles. After duplicates were removed, we conducted a title and abstract review for 647 citations, of which 225 were excluded. We compared the remaining 422 articles against 146 full-text articles listed in two systematic reviews that were identified early as the gold standard: a review by Snowsill et al., which was relevant to effectiveness and cost-effectiveness (Q1, Q4)(19); and by Usman Ali et al., which addresses harms (Q2).(20) We did not undertake a full-text

extraction for these 146 articles (as it was deemed unnecessary to repeat the review process). They were maintained in an Endnote reference library.

We conducted a full-text review of the remaining 276 articles, of which 98 met the inclusion criteria. We identified 15 systematic reviews from 2009–2019, of which eight were contemporary; the remaining seven contained data that had been superseded (see Table 1). Systematic reviews are recognised as the highest level of evidence for addressing questions and directing policy decision-making about interventions and diagnostic tests such as LDCT screening.(21) Thus, we extracted the data from the eight systematic reviews and 90 articles. The Evidence Check team extracted the data from the relevant studies into Excel software. A PRISMA flowchart of the literature selection process is included as Appendix 3.

Evidence grading

Quality ratings for major trials were already reported in an existing systematic review (please refer to Figure 1 in the Findings). Articles about program components (Q3) were reviewed using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool(22) for quantitative studies; the Critical Appraisal Skills Programme (CASP) qualitative research checklist was used for those studies that exclusively reported qualitative data.(23) Articles about cost-effectiveness (Q4) were rated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) scale.(24) Quality ratings are provided in Appendix 4.

Table 1: Included and superseded systematic reviews identified by the search strategy

Author (year)	Effectiveness	Harms	Cost-effectiveness	Smoking cessation	Clinical guidelines
Included reviews					
1. Huang et al. (2019)(8)	✓				
2. Iaccarino et al. (2019)(25)	✓			✓	
3. Snowsill et al. (2018)(19)	✓		✓		
4. Mazzone et al. (2018)(26)	✓	✓	✓		
5. Usman Ali et al. (2016)(20)	✓	✓			
6. Wu et al. (2016)(27)		✓			
7. Raymakers et al. (2016)(28)			✓		
8. Slatore et al. (2014)(29)				✓	
Superseded reviews					
9. Iaccarino et al. (2017)(30)				✓	
10. Pineiro et al. (2016)(31)				✓	
11. Coureau et al. (2016)(32)	✓	✓			
12. Li et al. (2016)(33)					✓
13. Humphrey et al. (2013)(34)	✓	✓		✓	
14. Manser et al. (2013)(35)	✓	✓	✓		
15. Bach et al. (2012)(36)	✓	✓		✓	

Findings

Question 1: What is the evidence for the effectiveness of lung cancer screening for higher-risk individuals?

The Evidence Check identified five systematic reviews of the effectiveness of low dose computed tomography (LDCT) lung cancer screening (hereafter 'LDCT screening'). The two most comprehensive systematic reviews of effectiveness were published in November 2018 (by Snowsill et al.) and July 2019 (by Huang et al.) and present the most contemporary synthesises of evidence.(19, 8)

A summary of LDCT screening trials is provided in Table 2, which lists the full trial name and acronyms used throughout the Evidence Check report. The systematic review by Snowsill et al. included studies from 12 trials published between January 2007 and January 2017. The systematic review by Huang et al. included studies from nine trials published to June 2019, including the latest results from the NELSON, MILD and LUSI trials.(37-39) Nine trials were considered eligible for review under the Evidence Check inclusion criteria; Table 2 shows these trials, including those that were reviewed by Snowsill et al. and Huang et al. More detail about the eligible trials is summarised in Table 3 (located at the report end).

Table 2: Summary of LDCT screening randomised controlled trials included in systematic reviews by Snowsill et al. and Huang et al.

Trial acronym or common name	Year trial commenced	Trial full name (or brief description where a formal name could not be identified)	Reviewed by Snowsill et al.(19)	Reviewed by Huang et al.(8)
Eligible trials				
NLST	2002	National Lung Cancer Screening Trial (US)	✓	✓
NELSON	2003	NEderlands-Leuvens Longkanker Screenings ONderzoek (the Netherlands & Belgium)	✓	✓
DLCST	2004	Danish Lung Cancer Screening Trial	✓	✓
DANTE	2001	Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays Trial (Italy)	✓	✓
ITALUNG	2004	Italian Lung Cancer Screening Trial	✓	✓
MILD	2005	Multi-centric Italian Lung Detection Trial	✓	✓
LUSI	2007	Lung Cancer Screening Intervention Trial (Germany)	✓	✓
UKLS	2011	UK Lung Cancer Screening	✓	–
Yang	2013	(Full name in English not identified) Community based lung cancer screening with LDCT in China	–	✓
Ineligible trials				
LungSEARCH	2007	Randomised controlled trial of surveillance for the early detection of lung cancer in a high-risk group	✓	–
Depiscan	2002	French randomised pilot trial of lung cancer screening comparing low dose CT scan and chest X-ray	✓	–
Garg et al	2001	Randomised controlled trial with low-dose spiral CT for lung cancer screening	✓	–
LSS-PLCO	2002	Lung Screening Study—The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	✓	✓

The search strategy identified a further 11 studies from included RCTs that were published after the Snowsill et al. systematic review (i.e. studies published after 1 January 2017). Five of these studies were subsequently included in Huang et al.'s review.(40, 37, 11, 38, 39) The remaining six studies are as follows:

- One study that presents NLST extended follow-up outcomes for incidence and mortality[41]
- One study that extends the MILD trial evidence specific to LDCT screening intervals[42]
- One study that presents pooled data from the MILD and DANTE trials[43]
- Three publications based on the NELSON trial data that are concerned with nodule count, characteristics and risk prediction.[44-46]

Australian LDCT screening studies

Two Australian LDCT screening studies are relevant to the Evidence Check. The Queensland Lung Cancer Screening Study (QLCSS) was a prospective observational study of LDCT screening at a single tertiary institution(47, 48) that was reported in 2015. The study aimed to test the feasibility of applying the NLST screening protocol in the Australian setting. Modifications to the protocol included a change in the age range (from 55–74 years to 60–74 years) and a test of minimal lung function. Participants had a baseline and two annual incident scans and were followed for five years. While the study had a small sample size (n=256 initially enrolled), it did demonstrate feasibility for detecting a high number of early stage lung cancers. The results identified rates of early stage cancers similar to the NLST (QLCSS: stage IA 58%, stage IV 8%; NLST: 52% and 13%, respectively), noting that 10 of 12 screen-detected cancers were stage I-II, nine of which were treated by surgical resection. In terms of attracting high-risk participants, the QLCSS is relevant because the study sample had higher self-reported occupational exposure to asbestos than the NLST; however, a 'volunteer bias' was evident, with more well-educated white males participating, suggesting participants did not represent Australia's diverse ethnic background. The advertising for the trial explicitly mentioned asbestos, which is relevant to the tailoring of recruitment strategies for LDCT screening.

The International Lung Cancer Screening Trial (ILST) is currently in progress and is a multicentre prospective cohort study that has dual aims: i) to define the optimal selection criteria for LDCT screening for the Australian setting, and ii) to evaluate pulmonary nodule management using the PanCan nodule malignancy risk model.(49, 50) At the time of the Evidence Check, we identified one article and one conference abstract that describe background information for the trial.(49, 50)

The ILST will recruit 4000 participants across Australia, Canada and Hong Kong; recruitment will likely close by December 2019. The trial uses an algorithm for the sampling design (see Table 4 below). The following direct quote explains the approach: *"Individuals in cells B, C and D, receive two annual LDCT scans and are followed for 6 years. Individuals who were invited to participate in the study and are negative by both criteria (cell A) will not receive LDCT screening, but samples of A will be followed for the occurrence of lung cancer. In comparing the detection of lung cancers and the number enrolled by USPSTF [US Preventive Services Task Forc]) versus* $PLCO_{m2012}$ *criteria, both criteria agree on excluding individuals in cell A and including individuals in cell D. The informative data for comparison are in cells B and C. McNemar's method can be used to compare if the number of participants or lung cancers differs between cells B and C. The NLST and CMS eligibility criteria are nested in the USPSTF criteria, so comparative evaluation of those criteria will also be made. In addition, sensitivity, specificity and PPVs [positive predictive values] will be compared."*(50)

A manuscript of the study protocol is currently under revision (personal communication, Dr Henry Marshall, 18 September 2019). It contains a number of secondary aims and sub-studies that will evaluate factors such as cost, impact on health-related quality of life (HRQoL), optimal screening strategies for smoking cessation, testing different recruitment methods (electoral roll versus primary care-based recruitment) and data about incidentally detected diseases. These data will take some years to be reported but will likely provide the next major evidence update about LDCT screening feasibility in Australia.

Table 4 Sampling schema for the ILST

Criteria status	USPSTF-ve	USPSTF+ve
$PLCO_{m2012}$-ve	a/A	b/B
$PLCO_{m2012}$+ve	c/C	d/D

A, B, C, D, number of individuals in each cell; a, b, c, d, number of lung cancers in each cell; $PLCO_{m2012}$, lung cancer risk prediction model described in reference.(51) USPSTF, US Preventive Services Task Force criteria described in reference.(52)

Lung cancer mortality

Low dose computer tomography screening has shown statistically significant mortality benefits in high-quality trials (NLST and NELSON).(8) The NLST demonstrated that annual LDCT screening reduced mortality by 20% compared with controls(5) while the NELSON trial showed an even greater reduction of 26% (95% CI, 0.46–1.19) in lung cancer mortality.(37)

The NLST extended follow-up analysis (median 12.3 years) demonstrated sustained reduction in lung cancer deaths in the LDCT arm, with a number needed to screen (NNS) to prevent one lung cancer death of 303(41), compared with the original estimate of about 320.(5) In terms of lives saved with LDCT screening, this is consistent with other analyses, which suggest three lung cancer deaths are prevented per 1000 persons screened.(53, 26, 54) In comparison, for colorectal cancer (CRC) the NNS was calculated as 1176 in 2007(55); projections for 2020 using microsimulation modelling estimates the NNS as 647–788 per death prevented, with 52–59 colonoscopies per death prevented (and CRC screening is highly cost-effective).(56)

While official publication of the full NELSON trial outcomes are awaited, the most recent NELSON outcomes data presented at the 2019 World Conference on Lung Cancer (7–10 Sept 2019, Barcelona, Spain) indicated a hazard ratio for lung cancer mortality of 0.74 (95% CI: 0.46–1.19, p=0.21) over an average observation time of 8.8 years (personal communication, Emily Stone, 8 September 2019). In terms of the most recent NLST published mortality outcomes, dilution-adjusted analysis of extended follow-up data (only deaths with diagnosis through study year six) demonstrated that there were 578 lung cancer deaths in the LDCT arm compared with 646 in the chest x-ray (CXR) arm, giving a lung cancer mortality RR of 0.89 (95% CI: 0.80–0.997, p=0.043).(41)

Smaller European trials are not sufficiently powered alone to detect statistically significant differences in mortality. Pooled data analysis provides opportunity for assessment of the expected benefit of LDCT that is unable to be detected via the analysis of individual studies.(57) Snowsill et al.'s analysis of four RCTs (DANTE, DLST, MILD, NLST) found LDCT screening was associated with a non-statistically significant decrease in lung cancer mortality (RR 0.94, 95% CI 0.74–1.19) with up to 9.8 years of follow-up when compared with controls, but with moderate heterogeneity (I^2 = 43.3%).(19) With the removal of the MILD trial(58), determined to be of low quality, the results demonstrated a statistically significant decrease in lung cancer mortality (RR 0.85, 95% CI 0.74–0.98) in favour of LDCT screening, with considerably reduced statistical heterogeneity (I^2 = 6.9%). Huang et al. included recent NELSON(37), MILD(39) and LUSI(38) mortality results not included in previous reviews, to also demonstrate a statistically significant reduction in lung cancer mortality (RR 0.82, 95% CI 0.73–0.91), when controlled for quality.(8) Pooled results of LDCT screening effectiveness mortality outcomes are summarised in Table 5.

Gender differences

LDCT has demonstrated a reduction of lung cancer mortality in comparison with controls, regardless of gender.(8) Recent NLST and NELSON trial data have demonstrated a mortality reduction in women. Extended NLST follow-up demonstrated a non-statistically significant lung cancer risk ratio lower in women (RR=0.80) than in men (RR=0.95). Other post hoc analysis of the NLST mortality results demonstrated weak evidence of a differential benefit by sex, with women having a more protective effect from LDCT than men

(RR: 0.73 vs 0.92; P=0.08).(53) While recent NELSON trial 10-year outcomes noted a (non-significant) 41.8% lung cancer mortality reduction in a small subset of 2382 Dutch women(37), the Evidence Check notes these are preliminary data and the full results of the NELSON trial will provide an update. Whereas the German LUSI trial demonstrated a statistically significant reduction in lung cancer mortality among women (HR=0.31, 95% CI: 0.10–0.96, p=0.04) but not among men (HR=0.94, 95% CI: 0.54–1.61, p=0.81).(38)

Table 5: Pooled analysis of LDCT screening trials and reported effectiveness outcomes

Meta-analysis; Included trials	**Lung cancer specific mortality**	**All-cause mortality**
NLST(59, 41)	**Statistically significant reduction** 20.0% (95% CI: 6.8–26.7; p=0.004)	**Statistically significant reduction** 6.7% (95% CI, 1.2–13.6; (P=0.02)
NELSON(37)	**Statistically significant reduction** 26% (95% CI: 0.46–1.19, p=0.21) 39% females: (95% CI: 0.35–1.06) 26% males: (95% CI: 0.60–0.91)	Not reported at time of Evidence Check
Sub-group analysis: excluding low-quality trials		
Snowsill et al.(19) DANTE, DLCST, NLST	**Statistically significant reduction** (RR 0.85, 95% CI 0.74–0.98) (I^2 = 6.9%, p=0.341)	**No statistically significant reduction** (RR 0.95, 95% CI 0.89–1.00) (I^2 = 0.0%, p=0.783)
Huang et al.(8) NELSON, Yang, LSS, LUSI, ITALUNG, DLCST, NLST	**Statistically significant reduction** (RR 0.82, 95% CI 0.73–0.91)	Not reported

Screening intervals and lung cancer mortality

Across trials, the intervals between the first (baseline) and repeat scans has varied; the variations assist in attempts to define the optimal LDCT screening interval.(60) Evidence in this area is rapidly evolving. In terms of effectiveness associated with various LDCT screening intervals, based on findings from modelling studies, Mazzone et al. noted *"screening every 2 or 3 years appears to lower both the number of scans performed and the expected lung cancer mortality reduction to one-half or one-third that of annual screening"* (p973).(26) While current evidence has focused on annual repeat screening, studies including the ILST and NELSON will assist in resolving debate about optimal screening intervals to reduce lung cancer mortality.

Recent MILD trial outcomes demonstrated no benefit from screening on an every-other-year basis, with biennial LDCT achieving similar mortality reduction at 10 years.(42) Emerging evidence suggests prolonged screening (biennial) may be appropriate for screening participants with a negative result on baseline LDCT scan.(42) Further evidence is awaited from the NELSON trial, which is sufficiently powered and investigating the effect of variable screening intervals (1 year, 2 year and 2.5 year intervals). Initial results suggest a 2.5-year screening interval reduces the effect of screening, with a higher rate of advanced stage disease; however, a biennial screening regime after an initial screening round could be effective.(60)

Lung cancer incidence, stage distribution and nodule characteristics

Comparative analysis has shown LDCT screening to be associated with a statistically significant increase in lung cancer detection rate(19), which may indicate implications for the possibility of overdiagnosis. The NLST had a high false-positive rate of about 25% in the first two screening rounds.(5, 61) Overdiagnosis is a

well-recognised potential harm of LDCT screening and addressed further in Question 2 of this Evidence Check.

The NLST found greater incidence of lung cancer in the LDCT arm, (1.13; 95% CI, 1.03–1.23); however, it resulted in fewer cancer deaths.(5) Similar findings have been demonstrated in pooled analyses of RCTs.(43, 62) Such findings support suggestions that the acknowledged potential overdiagnosis risks may be counterbalanced by the benefit of being able to detect cancers at an earlier stage with LDCT screening, where the disease is potentially curable.(62)

Trials have consistently demonstrated that lung cancers identified through LDCT screening are at an earlier stage compared with those identified with usual care, where approximately two-thirds of cancers are of advanced stage at diagnosis.(63) Snowsill et al.'s pooled analysis showed statistically significant increases in early stage cancer detection (I and II) (RR 1.73, 95% CI 1.27–2.37; I^2 = 61%) compared with controls, with a corresponding statistically significant decrease in late-stage (III and IV) cancer.(19) Similarly, Huang et al's pooled results from seven trials showed an increase in detection of stage I cancers (RR 2.08, 95% CI 1.43–3.03).(8) The most recent results from the NELSON trial report that from a total of 29,736 baseline scans, there was an overall referral rate of 2.1% for suspicious nodules, detection rates between 0.8% and 1.0% across the rounds, and 69% of screen-detected lung cancer was found at stage IA or B.(37)

Differences in 'positive' nodule size thresholds contribute to significant variations in stage distribution and the proportion of positive scans between trials. Positive size thresholds for nodules detected via LDCT vary between trials, from ≥4 mm in the NLST trial to ≥5 mm for solid nodules in the LUSI, ITALUNG and UKLS trials, while the NELSON, DLCST and MILD trials all refer to size and growth based on volumetric measurements.(26)

Multiple variations between studies make it difficult to draw conclusions about the optimal nodule size threshold. Several RCTs have recently published retrospective evaluations of lung cancer risk in screening participants based on their baseline screen result. Recent NELSON trial studies have considered the relationship between nodule count at baseline and lung cancer probability(44), as well as any relationship associated with new nodules' characteristics and count during incidence screening.(45, 46) Findings indicate that lung cancer probability does not significantly change with the number of nodules at baseline, nor does baseline nodule count help to differentiate between benign and malignant nodules.(44) Whereas new nodules detected through screening have limited association with lung cancer, the *"new solid nodule volume and, therefore, speed of growth is the strongest predictor for lung cancer"*.(45)

All-cause mortality

The NLST demonstrated a statistically significant 6.7% relative reduction (RR 0.94, 95% CI 0.88–0.998) in overall mortality with three rounds of annual LDCT over 7.4 years.(5) Using this NLST data, Usman Ali et al. calculated that the number needed to screen using LDCT to avert one death from any cause was 219 (95% CI: 115–5556).(20) An extended NLST follow-up analysis (median 12.3 years) demonstrated no statistically significant reduction in all-cause mortality in the LDCT arm compared with the CXR arm. The analysis demonstrated an overall mortality risk ratio of 0.97 (95% CI:0.94–1.01), with a difference across arms in the number dying (per 1000) of 4.2 (95% CI:-2.6–10.9, p=0.18).(41) Aberle et al. note that the lack of statistically significant effect should not detract from earlier demonstrated significance and may relate to an analysis window too long a period after screening.(41)

Snowsill et al. reported that LDCT screening compared with controls (usual care or best available care [CXR]) demonstrated no statistically significant increase in all-cause mortality outcome (RR 1.01, 95% CI 0.87–1.16) with up to 9.8 years of follow-up, but with substantial heterogeneity between studies (I^2 = 57%).(19) Huang et al. pooled seven RCTs and also demonstrated no effect on all-cause mortality (RR 0.95, 95% CI 0.90–1.00), with no heterogeneity with this outcome (I^2 = 0%).(8)

Quality ratings of major LDCT screening trials evaluating effectiveness

The Evidence Check includes existing quality ratings of major trials, as conducted by Huang et al. and shown in Figure 1.(8) Huang et al. used the Cochrane risk-of-bias tool criteria for randomised trials (RoB 2) to rate trials.(64) The majority of trials received an assessment of moderate to high quality although Huang et al. noted some concerns about low risk of bias for mortality outcomes. Two trials, DANTE and MILD, were both judged to be of low quality due to high risk of bias for mortality outcomes. The systematic review by Snowsill et al. conducted quality ratings for four trials (DANTE, DLCST, NLST and MILD) and similarly rated the DANTE and MILD trials as low quality(19) and noted that the MILD trial was at considerably greater risk of bias due to the randomisation process; concerns included lack of allocation concealment and marked differences in baseline characteristics. Baseline imbalances in the three other trials were noted as much less common and, when they did occur, were much less marked in size.(19)

The UKLS trial was excluded from Huang et al.'s review but included in the Snowsill et al. one. It was rated high quality using the Cochrane risk-of-bias tool for randomised trials (v1).(65) Huang et al. have queried the quality of the Chinese trial(11), citing uneven numbers between LDCT (n=3550) and control (n=3167) groups, which is not compatible with the 1:1 scheme randomisation reported in study methods, plus a limited follow-up (two years) that will potentially limit the power required for hypothesis testing.(8) Final results from this trial are yet to be reported.

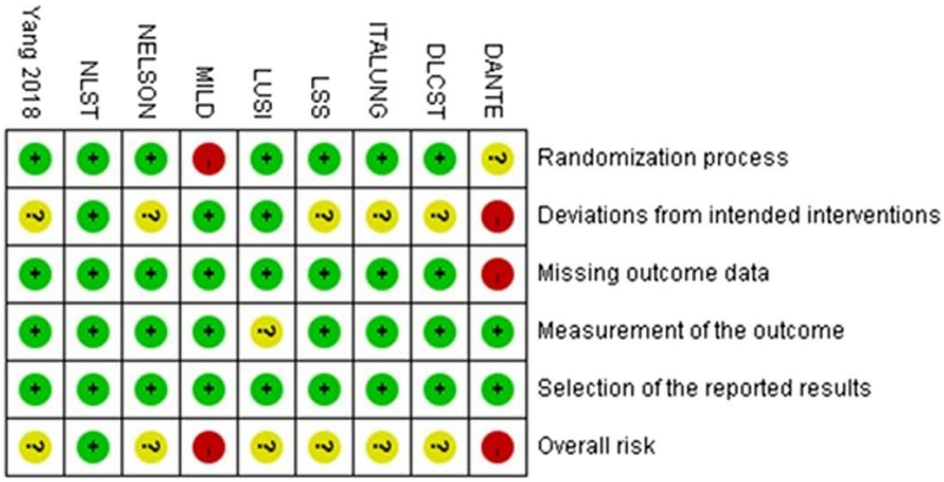


Figure 1: Risk of bias summary for included studies reporting mortality for nine included trials

(Note: red shading denotes high risk of bias, yellow shading denotes some concerns and green denotes low risk of bias). Reproduced with permission from Huang et al.(8)

Health-related quality of life (HRQoL)

Based on randomised evidence from four trials (NELSON, NLST, DLCST and UKLS), Snowsill et al. noted that the majority of trials demonstrate no statistically significant differences in HRQoL or psychological consequences between the LDCT screening group and control group at any point in time.(19) A systematic review by Wu et al. considered evidence from three large RCTs (NELSON, NLST, DLCST) and concluded there is potential for LDCT screening to cause short-term psychological burden in individuals with an indeterminate or positive scan result, but the adverse effects do not appear to have substantial long-term impact.(27) Psychological consequences and health-related quality of life are both considered potential harms associated with LDCT screening and are addressed further in Question 2 of this Evidence Check.

Smoking quit rates (smoking behaviour)

A combination of LDCT screening and smoking abstinence resulted in the maximum reduction in mortality in the NLST.(66) The combination of smoking abstinence and screening with three annual rounds of LDCT nearly doubled the reduction in lung cancer mortality (38%), compared with the reduction (20%) seen for individuals in the control group who abstained for seven years. Similar patterns for smoking cessation benefits were noted for overall mortality.(66)

A suggested potential drawback of LDCT screening is that it may induce a false sense of assurance and thereby negatively affect smoking abstinence.(19) High rates of current smokers in the NELSON trial final round of screening (six years post randomisation) could strengthen concerns that screening provides an unintended 'health certificate' to continue smoking.(60) However, findings from the UKLS trial indicate no evidence to suggest that a normal lung screen affects smoking abstinence.(67) Evidence suggests smokers with identified abnormalities on LDCT screening are more likely to stop smoking than those with normal results.(25) In a systematic review of patient-related outcomes of LDCT screening, Slatore et al. analysed outcomes of the NELSON and DLCST trials; the authors suggest LDCT screening itself does not influence smoking behaviours but may be associated with increased abstinence in those with suspicious findings on LDCT.(29) Smoking quit rates are discussed further in Question 2.

Risk of bias for psychological consequences/HRQoL and smoking behaviour

The systematic review by Snowsill et al. assessed four trials (DLCST, NLST, NELSON and UKLS) that contribute information about psychological consequences and HRQoL for risk of bias. The authors note a much greater risk of bias for these relative to mortality.(19) This was attributed to the subjectivity of outcomes resulting in the lack of blinding, losses to follow-up rates and the lack of clear reporting on study power to assess the outcomes in question. They note the UKLS was the only trial that demonstrated both good allocation sequence and allocation concealment but, unlike for mortality, the trial had no risk-of-bias issues with respect to baseline equivalence.(19)

The systematic review by Wu et al. acknowledges a lack of high-quality studies on screening-related psychological burden, noting that while trials provide some evidence of relevance, there is a high degree of heterogeneity in outcome measures used to capture psychological burden, plus the potential for bias in findings because trial participation itself might have psychological effects.(27)

For smoking behaviour, Snowsill et al. rated three trials (DLCST, NLST and NELSON) and found risk of bias was also much higher relative to mortality.(19) Again, elevated risk was attributed to the subjectivity of outcomes leading to a lack of blinding, losses to follow-up, and the lack of clear reporting on study power, with no risk-of-bias issues with respect to baseline equivalence.

Question 2: What is the evidence of potential harms from lung cancer screening for higher-risk individuals?

There are three systematic reviews that address the physical and psychological harms of LDCT screening, which are authored by Usman Ali et al.(20), Mazzone et al.(26) and Wu et al.(27) The first two reviews focus on the physical harms while the latter reports exclusively on psychological distress. The physical and psychological harms of LDCT screening are related both to the performance of the LDCT screening test and the consequences of evaluating abnormal test results. Commonly discussed harms include the physical and psychological consequences of evaluating LDCT screen-identified lung nodules.(20, 27, 26) The harms addressed in the two reviews include false positive results, morbidity and complications, mortality, overdiagnosis, exposure to radiation, psychological distress and impact on quality of life, and effects on smoking cessation.(20, 26) The review by Usman Ali et al. included 31 studies about harms published between May 2012 and 31 March 2015.(20) The more recent review by Mazzone et al. included 37 studies (16 studies overlapped with Usman Ali et al.) published up until August 2017(26), taking in harms data from major trials, including the NELSON, NLST, DANTE, DLCST, MILD and LUSI trials. The review by Wu et al. focused on the initial LDCT screen and examined short- and long-term psychological distress in studies published between January 2004 and January 2015.

Despite the evidence having been reviewed systematically, there remains limited data and a lack of high-quality controlled studies that assess the harms of LDCT screening. The studies examined in the systematic reviews include uncontrolled and observational study designs. Therefore, the evidence on the harms of LDCT screening is of low quality and caution should be exercised in the interpretation of results.

The Evidence Check search strategy identified a further seven studies (Table 6) published since the most recent systematic review cut-off date of August 2017. These individual studies include three microsimulation modelling studies, two retrospective cohort studies and two uncontrolled pre–post-test studies.(68-74) Both the Mazzone et al. and Usman Ali et al. reviews highlight the NLST as providing the highest quality data at this time. Therefore, the Evidence Check includes a detailed description from the NLST first in each of the subsequent sections.

Table 6: Additional studies since the publication of major systematic reviews that address the harms of LDCT screening

Authors Publication year	Study location	Study type	Harms
Han et al. 2017[70]	US (US Preventive Services Task Force)	Microsimulation modelling study	Overdiagnosis
Treskova et al. 2017[71]	Germany (German Health Update survey)	Microsimulation modelling study	Overdiagnosis
Rampinelli et al. 2017[72]	Italy (COSMOS study)	Retrospective analysis of data from an LDCT screening trial	Radiation exposure
Caverly et al. 2018[73]	US (The Veterans Health Affairs lung cancer screening demonstration project)	Microsimulation modelling study	False positives
Huo et al. 2019[74]	US (MD Anderson, Texas)	Retrospective cohort study	Major complications or morbidity from invasive follow-up testing
Dunn et al. 2017[75]	UK (UKLS pilot trial)	Pre–post-test	Psychological distress
Taghizadeh et al. 2019[76]	Canada (Pan-Canadian Early Detection of Lung Cancer Study)	Pre–post-test	Anxiety and HRQoL

False positives

A false positive result in LDCT screening is a positive screening result that eventually is diagnosed as a benign condition.(72) In the NLST(59), of the 26,309 patients who underwent LDCT screening, 6130 received at least one false positive result [23.30% (95% CI 22.79%–23.81%)]. Usman Ali et al.'s pooled analysis of three studies assessing false positive rates following a baseline LDCT scan(20) found that, of the 30,536 patients who underwent the single LDCT scan, 7619 patients received at least one false positive result [median 25.53% (range 7.90%–26.23%)]. Further pooled analysis of nine studies that assessed false positive rates of patients who participated in multiple rounds of LDCT scans found that of 43,943 patients who underwent multiple LDCT scans (> 1), 8469 received at least one false positive result [median 23.28% (range 0.64%–69.0%)].(20) The microsimulation modelling study by Caverly et al. assessed false positive rates between higher- and lower-risk patients and found a much higher false positive rate of 56.2%, which remained stable across all risk quintiles (95% CI, 53.1%–62.6% in quintile 1 compared with 51.9%–61.5% in quintile 5).(72)

Recommendations from NELSON trial analyses about nodule management, specifically nodule count and lung cancer probability, suggest all nodules be assessed on an individual basis in cases where more than one nodule is present on the scan result (about 51% of all scans).(44) The use of nodule risk-assessment models is discussed further in Question 3, including how these models help to reduce the rate of false positive screens.

False negatives

A false negative result in LDCT screening is a negative test result when the disease was in fact present.(19) The Evidence Check found the rate of false negatives to be a rarely documented harm of LDCT screening. Snowsill et al. note the percentage of false negatives scans in the LDCT screening arms of three trials range from 0.1%–1.3% (across NELSON, DANTE and MILD trials).(19) However, given the low-quality ratings for DANTE and MILD trials, the results should be interpreted with caution and updated following publication of the NELSON outcomes. The British Lung Health Check mobile screening van study (see Question 3 for a full description) reports a false negative result of 0.4% across 1337 scans (negative predictive value 99.6%, sensitivity 89.4% and specificity 97.1%).(75)

Invasive follow-up procedures following false positives

A consequence of false positive results in LDCT screening is patients undergoing unnecessary invasive follow-up procedures.(20) Invasive diagnostic procedures have previously been categorised by the NLST as 23 procedure types categorised into four groups: (1) cytology or needle biopsy, (2) bronchoscopy, (3) thoracic surgery, and (4) others.(5) Of the 26,722 people screened in the NLST, 183 individuals who had benign conditions underwent major invasive procedures, giving an absolute number of 6.85 patients (95% CI 5.93–7.91) per 1000 screened.(76)

Usman Ali et al. conducted their analyses by minor and major procedures, although procedure types were not defined.(20) Results from pooled analysis of eight studies indicated that of the 40,569 people who were screened, 403 patients with benign conditions underwent minor invasive procedures as part of diagnostic follow-up, resulting in an absolute number of 9.74 patients per 1000 screened (95% CI 4.34–15.15).(20) With regards to major invasive procedures as a result of LDCT-detected benign disease, pooled analysis of 17 studies found that of 66,535 patients who were screened, 411 patients with benign conditions were subjected to major invasive procedures as part of diagnostic follow-up, resulting in an absolute number of 5.28 patients per 1000 screened (95% CI 3.94–6.62).(20)

Mazzone et al. assessed only major procedures and defined these as any surgical resection by thoracotomy or video-assisted thoracoscopic surgery.(26) The pooled analysis of 17 studies (11 of which were also summarised by Usman Ali, 2016) reported that an absolute number of 4.7 per 1000 patients screened with

benign conditions underwent surgery (confidence intervals not reported).(26) Caverly's modelling study found 2% of all false positive results required downstream diagnostic evaluations (95% CI, 0.3%–2.6% in quintile 1 vs 1.7%–5.2%).(72)

Post-procedural complications

Post-procedural complications (or morbidity) are associated with invasive follow-up procedures as a result of positive findings from LDCT screening. The NLST reported that, of those who underwent invasive follow-up procedures as a result of positive LDCT screening, 78.14 per 1000 patients experienced major complications (95% CI 63.56–95.73).(5)

The estimated the rates of complications associated with invasive follow-up procedures performed for patients who had positive findings from LDCT screening are addressed by Usman Ali et al.(20, 26, 73), Mazzone et al.(26) and one additional study by Hou et al.(73) While Usman Ali et al. did not categorise minor and major complications, the authors analysed data for post-procedural major complications (undefined) and infections separately. A pooled analysis of four studies that assessed rates of post-procedural complications found that of 1465 patients who underwent invasive follow-up procedures as a result of positive LDCT screening, 109 had major complications or morbidity, giving an absolute number of 52.03 per 1000 patients who experienced major complications (95% CI 15.77–88.28).(20)

With regards to major complications within the total screened cohort, the NLST trial reported a rate of 3.19 per 1000 patients screened (95% CI 2.58–3.95)(20), whereas Mazzone et al. reported rates of 0.8 and 1.9 major complications per 1000 patients screened.(26)

Post-procedural mortality

The most serious potential harm is the risk of death as a result of invasive diagnostic procedures to evaluate an LDCT screen-detected nodule.(26) Most studies define post-procedural mortality as *"30 or 60 day post-operative mortality or mortality due to post-operative complications"*.(20) Mazzone et al. notes the difficulties in definitively determining if a reported death (after a procedure) was due to that procedure or an unrelated event that occurred after the procedure was performed. This should be taken into account when considering the interpretation of the following results.

The NLST reported 14.88 per 1000 patients died following invasive follow-up procedures (95% CI 9.18–24.04) and an absolute number of 0.61 post-procedural deaths per 1000 patients screened within the total screened cohort (95% CI 0.37–0.99).(20) In a pooled analysis of seven studies that assessed rates of post-procedural mortality Usman Ali et al. noted 20 deaths were reported for 1502 patients who underwent invasive procedures following LDCT screening, equivalent to an absolute number of 11.18 deaths per 1000 patients (95% CI 5.07–17.28).(20) Similarly, Mazzone et al. reported pooled results from six studies (five studies overlapped with those included in Usman Ali et al.) and found an absolute number of 7.7 deaths per 1000 patients who underwent invasive follow-up procedures (no confidence interval reported).(26)

Exposure to radiation

Patients are exposed to ionising radiation during an LDCT scan. Patients enrolled in a LDCT screening program may undergo multiple LDCT scans, as well as diagnostic CT and PET scans for the evaluation of any screen-detected nodules.(26) The level of harm from radiation exposure to patients in an LDCT screening program is dependent on the age at which the screening begins, gender, number of scans received, the CT technology and techniques used, and exposure to other sources of radiation; however, long-term studies of radiation exposure in LDCT screening are lacking.(70, 26)

Studies that assess the risk of radiation-related lung cancer mortality and radiation-induced cancer are summarised by Mazonne et al.(26) In a modelling study, the lifetime attributable risk of radiation-related lung cancer mortality, assuming annual LDCT examinations from age 55 to age 74 years, was estimated to

be approximately 0.07% for males and 0.14% for females.(77) Similarly, a study examining cumulative radiation exposure from 10 years of annual LDCT screening found the risk of induced major cancers was 2.4 major cancers theoretically induced over 5203 patients (0.05%), with a higher risk noted for women, attributed to the increased radio-sensitivity of females and to the risk of breast cancer associated with chest CT scans.(70)

As with many of the potential harms reported, refined patient selection criteria using radiation risk models combined with the recent advances in LDCT technology will further reduce the radiation exposure risks to patients.(78, 70, 26)

Overdiagnosis

Overdiagnosis is associated with unnecessary treatment, exposing patients to invasive procedures and costs that impact negatively on wellbeing and life expectancy.(69, 26) However, definitions and thresholds for overdiagnosis vary across studies. Overdiagnosis is defined by Mazzone et al. as a patient with a screen-detected lung cancer that is indolent or clinically insignificant".(26) Snowsill et al. define it as *"when a disease is detected by screening that would not have clinically presented prior to death from other causes in the absence of screening (p.xxi)"*.(19) Given the difficulty in defining clinically insignificant tumours, some definitions include any screen-detected lung cancer (indolent or aggressive) in a patient with a comorbid condition that will lead to their death before the cancer would have affected their wellbeing.(69) Despite discrepancies in definitions, the reviewed studies highlight the importance of selecting patients for screening who are without particular comorbid conditions that cause a high risk of mortality overshadowing the risk of lung cancer as a potential cause of mortality in the future.

Snowsill et al. note most LDCT screening trials do not report relevant data about overdiagnosed lung cancers attributable to screening.(19) The authors note that the *"adequate length of follow-up is of particular importance for quantifying the degree of overdiagnosis in cancer screening"*. However, the *"optimum duration of follow-up for measuring overdiagnosed lung cancers is not known"*.(19) In the NLST, the rate of overdiagnosis among all LDCT screen-detected tumours was 18.5% (95% CI: 5.4–30.6).(79) Another key finding of the NLST was the particularly high overdiagnosis rate for lepidic predominant adenocarcinomas detected by LDCT at 78.9% (95% CI: 62.2–93.5); it was suggested this was due to the slow growth rate of tumours that begin as pure ground-glass nodules.(26) Usman Ali et al. summarised four studies that assessed rates of overdiagnosis from all LDCT screen-detected tumours and reported that estimates ranged from 10.99%–25.83%.(20)

A modelling study by Han et al. that compared 576 screening eligibility scenarios by age range, screening frequency and pack-years of smoking, found overdiagnosis was higher for more frequent screening, older starting age and stopping age, and higher smoking pack-years.(69) For example, when modelled for a stopping age of 80, the model median range was 4.73%–13.71%, and with a stopping age of 75, the model median range was 3.91%–10.72%. Furthermore, the refinement of nodule management thresholds are imperative to reducing overdiagnosis. A modelling study that reported increased nodule size for follow-up using NELSON-like scenarios (from a volume of 50mm^3 to 80mm^3) and using NLST-like scenarios (from a diameter of 4mm to 5mm) led to a 5% and 4% decrease in overdiagnosis, respectively.(71)

Psychological distress and quality of life

Three systematic reviews synthesise the available evidence from a small number of relevant studies about the measurement of psychological distress and quality of life in participants of LDCT screening programs.(20, 27, 26) The Evidence Check identified two additional studies published after the Wu et al. review.(68, 74) The distress and quality of life measurement tools examined in systematic reviews and additional studies include the Short Form questionnaire (versions SF-12, SF-36), European Quality of Life measure (EQ-5D), the State-Trait Anxiety Inventory (STAI-20), Impact of Events Scale (IES), Consequences of

Screening (COS) and Consequences of Screening in Lung Cancer (COS-LC) and the Psychological Consequences Questionnaire (PCQ).(27)

There is potential for patients to experience psychological distress or reduced health-related quality of life (HRQoL) at any point along the screening pathway due to factors including the nature of the result, requirement for further testing and the individual's own psychosocial characteristics.(80) A diagnosis of lung cancer can cause significant distress and can induce anxiety in those with an indeterminate result for an LDCT screen-detected nodule.(81, 26) Evidence suggests LDCT screening may be associated with short-term adverse psychological harm, particularly after a false positive result, but does not have a substantial long-term impact.(27) Increased lung cancer-specific distress was reported in NELSON and UKLS trial participants with an indeterminate result.(82, 83) However, the adverse psychological effects diminished or resolved at follow-up, suggesting the distress was only experienced short-term.

The study by Dunn et al. (n=1589) found patients who required follow-up after their initial screen were most concerned about their result.(68) Levels of concern were particularly high for patients who had initially expected a negative screening result pre-screen, were of low socioeconomic status, older age and had less experience with lung cancer. The study by Taghizadeh et al. (n=1237 participants) found clinically significant increased anxiety following the initial LDCT screen was more common among females and participants who were concerned about getting lung cancer prior to screening.(74)

While evidence suggests no long-term adverse effects on psychological distress and HRQoL, the transient increase in psychological distress experienced by those with a positive or indeterminate LDCT finding suggests individuals with unexpected results may benefit from additional support during the screening process.(68) Future LDCT screening programs would benefit from further high-quality research to determine the frequency, duration and scale of psychological distress plus the impact on HRQoL (outside trial settings).

Impact on tobacco control and smoking cessation

Current evidence is conflicting regarding whether undergoing LDCT screening in and of itself motivates smokers to quit.(26) As previously discussed in Question 1 of this Evidence Check, there is no evidence to suggest a normal lung screen influences smoking abstinence or motivation to quit(83) and quit rates are greatest in participants who receive a positive screen result.(29) Furthermore, evidence from the NELSON and DLCST trials found no difference in smoking cessation rates between LDCT screening and control groups, further confirming that LDCT screening does not adversely affect smoking abstinence.(26) Incorporation of smoking cessation has become a mandated component of screening programs in the US setting.(84) The implementation of smoking cessation in LDCT screening programs is explored in Question 3 of this Evidence Check.

Communication about the harms of screening

Communicating the benefits and harms of LDCT screening can be challenging for the public, patients and healthcare providers. An infographic has been developed very recently by the International Agency for Research on Cancer to demonstrate the potential benefits and harms of LDCT screening using updated NLST data that includes more precise estimates based on the Lung-RADS nodule classification (Figure 2). This infographic is included in the Evidence Check to indicate how communication about harms might be included in future 'real-world' LDCT screening programs.

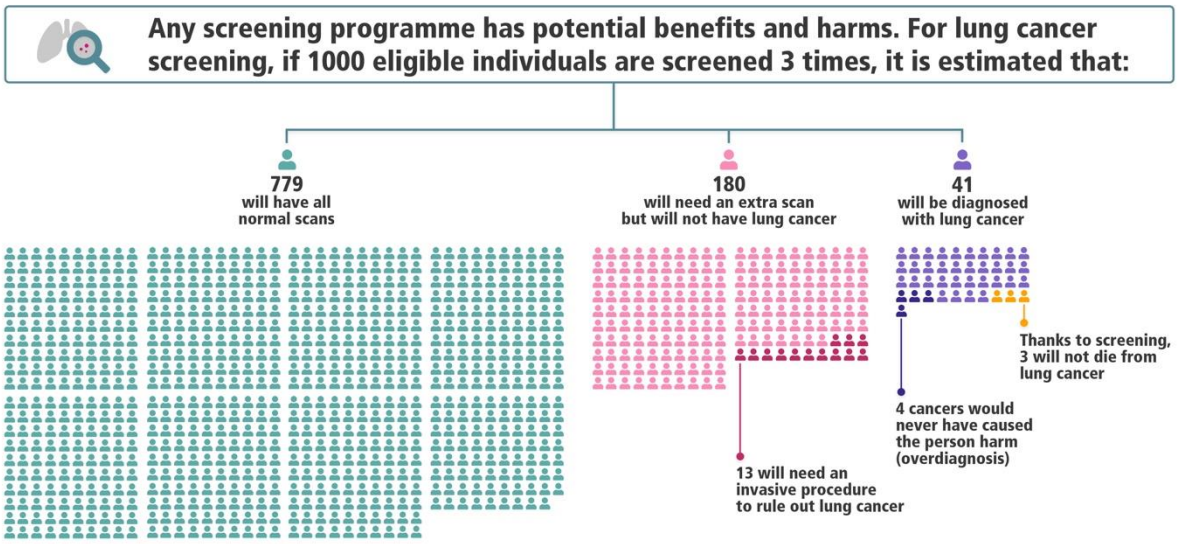


Figure 2: Infographic depicting estimated outcomes in the US National Lung Screening Trial under the Lung-RADS nodule management protocol

Reproduced with permission from the International Agency for Research on Cancer; full-page infographic available at https://www.iarc.fr/infographics/benefits-and-harms-of-lung-cancer-screening/

In summary, LDCT screening has led to an increase in the frequency of invasive diagnostic procedures and the number of resulting complications, morbidity and mortality following the invasive procedures. However, these harms must be considered in balance with the potential benefits. Further minimising potential harms requires careful design delivery of LDCT screening program components including patient selection, effective communication about the results of screening, the use of nodule management models and the judicious use of invasive procedures to evaluate and treat screen-detected nodules and cancers.(69, 26, 50)

Question 3: What are the main components of recent major lung cancer screening programs or trials?

There are no systematic reviews that synthesise evidence about the main components of recent major lung cancer screening trials and programs. Two systematic reviews specific to smoking cessation as a component of lung cancer screening programs have been published(31, 85) and are discussed at the end of Question 3.

The search strategy identified evaluation studies of 'real-world' program implementation in single institutions or across multiple sites (as the major trials had already been identified in Q1 and Q2 strategies). The breadth of available evidence sources was spread across journals in health services research, lung cancer, radiology and quality management. The Evidence Check inclusion criteria did not originally extend to clinical practice guidelines or policy statements and an extensive search of the grey literature was not in scope. However, key policy documents became an essential inclusion as they define the protocols and standards to which LDCT screening programs must adhere. This is particularly evident in the US, where 'real-world' programs have been implemented based on the US Preventive Services Task Force statement(52), published in December 2013, and the Centers for Medicare & Medicaid Services (CMS) decision memo(84), published in 2015. The implications of these statements are discussed in the narrative.

Search strategy

The search strategy (2009–2019) identified a wide range of relevant studies:

- Original studies (n=31): program evaluations and surveys with healthcare providers and health services about program components (featured in studies from high-income countries); these studies are summarised in Table 7 (located at the report end)
- Published policy statements and clinical practice guidelines (n=9) that specifically discuss how to plan and implement an LDCT screening program. Seven documents are from the US and one each from the UK and Europe. These are summarised in Table 8 below.
- Original studies specific to smoking cessation programs within the LDCT screening program setting; of these, one new study(86) was identified and the remaining four are reported(87-90) in the two systematic reviews(31, 85); refer to Table 12 (located at the report end).

We identified an additional 54 publications:

- Literature reviews (non-systematic) and commentaries about program components and the barriers and facilitators to implementation (n=17) and smoking cessation (n=3)
- Studies of the beliefs, attitudes and opinions of the public and healthcare providers about LDCT screening (n=15)
- Studies about strategies to improve shared decision-making, including one RCT (n=7)
- Study protocols about implementation initiatives (n=5) and smoking cessation (n=1)
- Focus group or textual analysis of awareness campaigns (n=2)
- Anxiety and depression interventions (n=2) or assessing anxiety and quality of life outcomes (n=1)
- Modelling studies about screening benefits (n=1) and a review of models used across RCTs (n=1).

We did not extract the data as these studies did not fall into the scope of Question 3. The summary is provided to show the breadth of contributing literature about LDCT screening. Two studies were conducted in the Australian setting, including a study by Flynn et al., who surveyed current and former smokers in one respiratory clinic (n=90) about their attitudes and willingness to participate in an LDCT screening program and to undergo surgical treatment.(91) A study by Manners et al. surveyed 93 general practitioners from Western Australia about current lung cancer screening practices.(92)

Table 8: Published policy statements and clinical practice guidelines on LDCT screening implementation

Country	Policy statement or clinical practice guideline abbreviated name	Source
US	US Preventive Services Task Force (USPSTF) recommendation	(52)
	Centers for Medicare & Medicaid Services (CMS) decision memo	(84)
	American Thoracic Society and American College of Chest Physicians policy statements on implementation of LDCT screening	(93-95)
	American College of Radiologists: Appropriateness criteria for LDCT screening	(96)
	American College of Chest Physicians: Clinical Practice Guidelines	(97)
	American Thoracic Society and American Lung Association: Implementation guide	(98)
UK	NHS policy document: Targeted screening—standard protocol	(99)
	British Thoracic Society quality standards for the investigation and management of pulmonary nodules	(100)
Europe	European Respiratory Society (ERS) white paper	(101)

Study types and quality

The original program evaluation studies are mostly single-institution evaluations (n=10) of US LDCT screening programs.(102-111) Three US studies evaluate programs at multiple sites: Kinsinger et al. report on eight Veterans Health Administration (VHA) sites(112); Gould et al. report on four integrated healthcare

systems of the Cancer Research Network, funded by the National Cancer Institute(113) and Gesthalter et al. conducted a qualitative evaluation at three VHA sites.(114) In the UK, a pilot evaluation of mobile LDCT screening vans in deprived areas of Manchester was reported on twice by Crosbie et al.; these studies reported on clinical and process outcomes at baseline and a second screening round.(75, 115)

Most of these original studies did not use randomised designs. This is not surprising since the intention is to report on initial experiences of implementing a 'real-world' LDCT program. Hence, most studies are descriptive and use quantitative, qualitative or mixed-method designs. Most evaluations have been published since 2017, which reflects the time lapse from program establishment, implementation and through to collecting evaluation data for any LDCT screening program. The Evidence Check also identified six studies that conducted surveys with US participants about one or more aspects of program components including: recruitment(116); characteristics of and barriers to LDCT screening (n=65 centres)(117); a survey of community-based LDCT screening centres(118); patient perspectives from a VHA program(119); federally qualified health centres about disparities in offering LDCT screening(120); and one about eligibility and inappropriate screening.(121) Several studies focused on documentation in medical records, including smoking history, all from the US.(122-125) One study from Korea assessed the feasibility of implementing a radiology lung imaging reporting and data system.(126)

LDCT programs or pilot studies by country

A summary of programs and trials from high-income countries was compiled from multiple sources, including a non-systematic review by Pinksy(127) (see Table 9). Numerous studies listed by Pinsky did not meet the Evidence Check inclusion criteria as the primary sources were protocols or conference abstracts.

Across high-income countries, a variety of health service models are used to deliver LDCT screening, including centres of excellence, hub and spoke models (centralised radiological readings of LDCT scans with community-based screening) and LDCT mobile screening vans. The British approach differs considerably from US models; British LDCT screening is promoted as a 'Lung Health Check' (LHC) to overcome the documented barriers attracting current smokers and people from lower-SES backgrounds(128-132) to participate in LDCT screening.(115) The LHC holistic approach was nurse-led and focused on lung health to include spirometry (lung function test) being offered to all participants. The mobile screening van was located at a local shopping centre(75) to overcome the known barriers of travel and accessibility/convenience.

The beliefs and attitudes about LDCT screening as a barrier to participation are also described in the US literature(133-136) and have informed policy decisions about recruitment and shared decision-making (discussed below).

Table 9: LDCT screening programs and pilot studies in high-income countries

Country	Trial, pilot or program	Sources
US	NLST and over 2000 LDCT screening centre programs across the US	(5), (102-111)
Canada	The Pan-Canadian Early Detection of Lung Cancer [PanCan] study *(NB. This study is not included in the main RCT section as this is a single arm prospective study that developed a predictive risk model).* Four pilot studies (Ontario, British Columbia, Alberta, Quebec). For example, Cancer Care Ontario (CCO) launched a pilot-organised LDCT screening program in 2017 across four hospitals.	(137, 127)
Europe	NELSON, DLCST, DANTE, MILD and LUSI trials (as described in Q1) Programs were identified for Spain and Poland but studies did not meet the Evidence Check inclusion criteria	(138, 139)
UK	UKLS; LSUT (Lung Screen Uptake Trial) pilot study: Mobile screening vans	(140, 80, 75, 115, 141)
Australia	QLCSS study and ILST trial	(47, 48, 89)

		(49), (50)
New Zealand	No pilot studies or programs; cost-effectiveness study is included in Q4	(142)
East Asia	LDCT trials are underway in China, South Korea, Hong Kong; Japan and Taiwan have implemented ad-hoc programs in the past	(50, 11, 126)
South America	First Brazilian Lung Cancer Screening Trial (BRELT1) was initiated in 2013 in greater Sao Paulo	(143, 127)

Variations in uptake of LDCT screening pilot studies and programs

There are considerable variations in the uptake of LDCT screening programs across international studies. In the British pilot of mobile screening vans, Crosbie et al. recruited participants (n=2541) from 14 primary care practices in Manchester and reported extremely high demand, with all appointments booked out within a few days. Essentially all participants (99.5%) consented to data inclusion in a research database.(115) High uptake was maintained over time, with screening uptake reported as 90% in second-round results.(75)

This uptake is in stark contrast to US reports of low participation in LDCT screening. Estimated uptake as reported across program evaluations and surveys ranges from 4%–58%. For example, Kinsinger et al. report that 58% of veterans agreed to participate in LDCT screening across eight VHA sites.(112) The authors did not collect data about reasons for refusal to participate in screening. Low participation rates were also reported in other US evaluations(104, 144), including that a rate of 4% of 6.8 million eligible US citizens were being screened, based on 2010 and 2015 National Health Interview Survey data (n=2167).(145) However, these data should be interpreted with caution as they were estimates from surveys (rather than directly reported data from LDCT screening programs) and did not meet the Evidence Check inclusion criteria.

Reasons for low uptake include that LDCT screening is a relatively new innovation and not routinely offered (i.e. lack of patient awareness) and difficulties in attracting patients to screening programs.(117) Lack of primary care physician awareness of LDCT screening and referring people likely to be eligible, as well as lack of information about the cost of the screening test and uncertainty about reimbursement are cited consistently across the literature.(103, 117, 107) A summary of barriers across the major components of programs is summarised in table 10. Across all studies there was a consistent message about the challenges and complexities of establishing LDCT screening programs to attract people at high risk who would receive the greatest benefits from participation. Implementation of program components was described as complex and fraught with challenges and barriers(114, 112) that required significant infrastructure and careful planning.

Table 10: Common implementation challenges/barriers and facilitators/enablers

Implementation challenges/barriers
Recruitment, eligibility, selection and referral of the high-risk population • Variations in recruitment methods(144) • Costs associated with recruitment methods(146) • Targeted recruitment of minority populations may be more expensive and time-consuming than recruitment of general population(116) • Poor (absent and inadequate) documentation of smoking behaviours and smoking history(103, 147, 113, 112, 144, 125, 110) • Difficulties with electronic tools and accessing relevant clinical data for identifying eligible participants(112, 123) • Lack of provider awareness (e.g. lack of awareness of screening availability, patient eligibility)(103) • Lack of provider referral and changing referral habits(117, 148, 144, 118) • Patient anxiety and stigma associated with smoking and lung cancer risk(110) • Lack of patient awareness about screening availability(107, 118) • Difficulties attracting participation / low patient demand(117) • Issues or uncertainty about cost regarding insurance coverage(103, 118) **Education of the public, people at high risk, healthcare providers** • Limited time for shared decision-making(110) • Lack of community education(117) • Provider reluctance and lack of 'buy-in', e.g. primary care providers not convinced about validity of LDCT screening(117, 114) **Delivery of a screening program** • Billing or coding issues to ensure reimbursement(117, 110, 118) • Multiple guidelines with variations(110) • Staff workload and workflow issues(114, 118) • Ensuring patients receive appropriate follow-up and scheduling of subsequent screening examinations(117, 105)
Implementation facilitators/enablers
• Electronic health record (EHR) alerts for proactive scheduling of LDCT scans(103), or visit-based reminders(106) • Meetings with key stakeholders to encourage engagement and explain intake processes(106) • Educational events(103, 117, 114) • Nurse coordinator position to work across all program components, including preventing loss to follow-up (through register maintenance and directly contacting patients)(114, 105) • Multidisciplinary approach for review of screen results to generate treatment recommendations(117, 114, 105) • Identify program champions (e.g. physician director and nurse coordinator)(114) • Guidelines(117)

Table 11: A summary of major components of LDCT screening programs

Program components	Details
1. Recruitment, eligibility, selection and referral of the high-risk population	
Recruitment • Direct mailing, mass media and community outreach **Eligibility** • Agreed criteria based on core risk factors • Risk prediction models • Documentation of smoking history in the electronic medical record (EMR) and other systems **Selection for LDCT screening** • A national (or jurisdictional) registry of the high-risk population that includes robust electronic mechanisms to invite the cohort, enable systematic monitoring of screening uptake and registry maintenance • Information resource and consent process for high-risk population **Referral** • Examination ordering and processes for coordination of referrals for eligible participants	
2. Education of the public, people at high risk, healthcare providers	
Awareness campaigns • Education strategies for the public to build awareness of lung cancer and explain LDCT screening, benefits and harms • **Shared decision-making** • Consultation about LDCT and use of decision aids **Education of healthcare providers** • Awareness of LDCT screening (including effectiveness, benefits and harms, smoking cessation); targeted education for primary care providers	
3. Delivery of a screening program	
Planning phase • Governance, human resources, technological and infrastructure requirements • Ensuring the safe delivery of the screening program • Multidisciplinary team engagement • Navigator role: typically, specialist nurse who takes responsibility for practical aspects of screening and communication	
Implementation phase • Radiological interpretation of CT scans • Communication of tests results to the patient • Communication of test results to primary care physicians • Referral to treatment	
Maintenance phase • Data management • Quality assurance: reporting and audits of screening outcomes, compliance with protocols, radiology, treatment outcomes	
4. Data reporting and research	
Data reporting • Reporting outcomes to enhance international research into LDCT screening	
5. Smoking cessation	
Evidence review • Details of programs in high-income countries	

1. Identifying the high-risk population: recruitment, eligibility, selection and referral

Recruitment

The recruitment of potential high-risk participants from the general population is central to all LDCT screening programs. Three core strategies are used to attract participants: i) direct mailing of invitation letters and reminders, e.g. the LUSI trial(38); ii) mass media (advertising strategies using print media, radio, TV, social media), e.g. the MILD trial(58); and iii) community outreach, e.g. the UKLS trial.(115) There is wide variation in the recruitment methods used across trials. For example, the NLST protocol did not provide screening centres with any restriction or guidance on recruiting participants, leaving each centre to choose its own recruitment methods.(116) Marcus et al. surveyed coordinators from 22 NLST centres about recruitment methods; all indicated use of direct mailing, either through commercial mailing lists or healthcare system registries.(116) Recruitment strategies included public seminars and community outreach into places typically frequented by smokers, such as bars, pubs and clubs.(116) NLST recruitment costs varied from $US6–$325 per person; costs are rarely reported in trials or program evaluations.(116)

The direct mailing approach in other trials and programs has included the use of population-based registers or electronic health records (EHR) to identify potential participants for eligibility appraisal. Population-based registers have been used in the European and British trials to identify the target high-risk population. Invitation letters are then posted that encourage people to complete a questionnaire to establish their eligibility for LDCT screening. For example, the NELSON trial used a specific population-based register, initially recruiting Dutch men, and later men and women in Belgium.(149) The LUSI trial in Germany used population registers in the area around Heidelberg.(38) Enrolment rates from direct mailing have been reported as 4.5% for the ITALUNG and NELSON trials, which is higher than the 3.7% reported in the NLST.(116) The UKLS trial identified individuals from population Primary Care Trust records who would receive mailed questionnaires, achieving a favourable 30.7% positive response rate to the initial mailing.(140) However, only 3.5% of the total met eligibility criteria, which acknowledges the need for better strategies to target high-risk individuals. Similarly, potential participants have been flagged via the application of eligibility algorithms to electronic health records (EHRs), followed by clinician approach or mail-out of LDCT screening program information and shared decision-making (SDM) aids.(125, 108)

Mass media recruitment approaches go hand-in-hand with public awareness campaigns and are often a single component of a multifaceted recruitment strategy. For example, one study used a combination of primary carer referral, hospital marketing and local media opportunities, including an offer of financial discount on the LDCT cost for those without insurance.(107) Community outreach strategies include: clinician referrals, such as direct referral via primary care physicians, health centre check-ups, word-of-mouth and physical outreach into the community, such as mobile screening units.(116, 104, 150, 115) Recruitment methods typically involve raising awareness and knowledge of programs and therefore are discussed further in the following section addressing awareness campaigns and education targeting at-risk individuals and healthcare providers.

The translation of recruitment strategies from trial settings to real-world screening is challenging given ad-hoc approaches and a lack of data collected during large-scale trials. Within the trial setting, recruitment may be a funded component of the study design, whereas in real-world programs this may not be the case. In US screening programs, a lack of planning and agreement has been described and program managers may have limited information about people at high risk within the local population, limiting the ability to determine how best to target potential participants.(114) We note that evidence about recruitment from the ILST study is forthcoming; this study will report on strategies used in Western Australia to compare direct-mail invitations using the electoral roll with personalised invitations sent from general practices. Initial reports indicate that the latter strategy appears to have been more effective (personal communication with Dr KP Lim and A/Prof A McWilliams, respiratory physicians).

Eligibility

Determining eligibility for LDCT screening is fundamental to the success of defining a high-risk population in any setting. In the trial setting, age, smoking history and smoking status are the core criteria used to assess eligibility. Criteria are inconsistent across trials and variations have been introduced during translation from the trial setting to real-world programs. The best documented example is the adaptation recommended by the US Preventive Services Task Force (USPSTF) to increase the age range eligibility from 55–74 years (as per the NLST) to 55–80 years.(102, 104, 107-110)

Beyond the core eligibility criteria, additional factors are included in the creation of sophisticated risk algorithms known as multivariable risk prediction models. These models include criteria such as education, previous cancer diagnosis, family history of lung cancer, body-mass index and comorbidities such as COPD. Three of the best-known models are the $PLCO_{m2012}$ (an update of the original PLCO model); the PanCan model(137); and the Liverpool Lung Project (LLP) model that was used to select eligible candidates for the UKLS trial.(151) The PanCan risk prediction model was developed through a single-arm prospective study in Canada (which commenced in 2007, with five-year follow-up).(137) This study demonstrated that early stage cancers could be detected at a higher rate than in the NLST; i.e. 77% (133 of 172) of lung cancers in the PanCan study were early stage (I or II, $p<0{\cdot}0001$), compared with 57% in the NLST. The LLP risk model was based on a case-controlled study(152) and when applied in the UKLS, 85.7% of detected lung cancers were early stage I or II.(151) These models require validation in local populations using epidemiological measures. For example, the $PLCO_{m2012}$ model has been validated in the NSW setting using 45 and Up study data.(153) Risk prediction models are being further tested in trials and studies including the ILST.

In real-world programs, data to determine eligibility are sometimes included as a function of an EHR where patients are flagged, or an alert is created to check or confirm eligibility. These EHR flags have been implemented across many US health systems including the VHA(114, 112) and single institutions.(103, 113, 122, 148, 125, 111) Establishing eligibility is essential to program efficiency and to minimise potential harms associated with missed or inappropriate screening referrals. Therefore, planned education interventions for healthcare providers are required to ensure primary care and other specialist clinicians aware of eligibility criteria.(154, 123)

Determining eligibility: documentation of smoking history

A frequently reported challenge in determining participant eligibility is the accurate recording of smoking histories for potential participants.(147, 112, 106) For example, Kinsinger et al. described the challenges of finding documented histories in the sophisticated electronic medical records (EMR) system of the VHA.(106, 125)

Several studies have tested different methods for eliciting smoking histories.(122, 106, 125) In a study of five health centres, Modin et al. extracted pack-year smoking history from the EMR and compared this with the pack-year history obtained through a nurse-led shared-decision making (SDM) consultation.(122) There was a 96.2% discordance between the EMR and the SDM consultation, with an under-reporting in the EMR. This discrepancy would have resulted in more than half the screening participants not meeting the pack-year threshold for screening if relying on EMR data alone. Similarly, Cole et al. sought to assess the accuracy of the EHR information in comparison with patient self-report.(125) The study found the EHR was insufficient for determining eligibility for 30% of participants; however, the small sample size of 24 participants should be noted.(125) These examples are further supported by a retrospective cohort study of 12,801 patients in California by Li et al., which identified the lack of smoking history documentation as a significant barrier to *"enabling appropriate selection of high-risk individuals for screening"*.(155) These studies highlight the challenges of determining eligibility. The Evidence Check did not locate any Australian studies that provide a baseline about smoking history documentation for LDCT screening.

Selection

The process of selecting eligible participants requires dedicated infrastructure to be implemented across health systems. Selection strategies described in the literature include electronic mechanisms to invite the cohort, systematic monitoring of screening uptake, and the creation and maintenance of high-risk population registers.

A national (or jurisdictional) register of the high-risk population is strongly recommended for all LDCT screening programs.(99) Such registers have been designed for multiple purposes. First, participants' demographic eligibility status can be registered to ensure the program complies with agreed entry standards.(99, 98) Second, registers are used to track quality and clinical outcomes, such as: the number of diagnostic imaging tests and follow-up surveillance; non-surgical and surgical biopsies that are performed for malignant and benign screen-detected nodules; the number of lung cancer diagnoses, and the number of procedure-related adverse events, as well as descriptive information about cancers diagnosed (histology, stage, treatment and survival).(98) Registers can incorporate data collection about shared decision-making consultations, and whether smoking cessation interventions are offered. The NHS protocol also makes specific reference to the provision of information resources and consent processes(99); a register can similarly collect this level of data or link to EHR records.

Referral

Numerous studies document strategies and data management systems to ensure that an eligible participant receives an LDCT examination in a timely way. In the US literature, this is usually referred to as 'examination ordering' and there are some examples of how orders are processed. For instance, Begnaud et al. described the introduction of an automated EHR function to ensure physician-ordered CT examinations were automatically booked rather than leaving patients to initiate the scheduling process.(103) This automated function increased the number of completed scans from a baseline of 63% to 81% over a two-year period. Gould et al. similarly noted that using standardised order templates at three screening centres enabled more accurate tracking of when examinations had been performed; unique codes were used to distinguish between screening examinations, nodule follow-up and other diagnostic LDCT scans (no actual quantitative data were reported).(113) The examination order usually comes from the GP or respiratory physicians; in some US programs, the nurse practitioner has responsibility for ordering(110), typically through the EHR.(109),(148)

2. Education of the public, people at high risk, healthcare providers

Awareness campaigns

Public awareness campaigns, including education strategies that explain LDCT screening, benefits and harms, are acknowledged as a major component in improving screening rates among eligible participants.(146, 156) The key messages of campaigns typically encourage former or current smokers to discuss eligibility for LDCT screening with their healthcare provider.(157) Two studies noted a common theme portrayal of hope and survival to encourage participation, rather than messages stimulating negative emotions of shame, guilt and fear, which could adversely influence engagement.(146, 157)

Demonstrated methods include mixed-media approaches to community awareness campaigns, including use of small media (e.g. at fuel stations and convenience stores), radio, newspaper and digital media(157), as well as online educational content about screening and LDCT.(146, 156, 157) Other strategies include campaign information disseminated by a family doctor or specialty provider(146) and outreach activities direct into the community to increase awareness of screening.(94) Awareness campaigns associated with US state-based screening programs suggest digital campaigns have the potential to increase awareness of LDCT screening(157) and influence behaviour, with significant higher scheduled LDCTs during and after campaign periods.(146, 156)

Community outreach by LDCT screening programs may be especially important to reach high-risk individuals from disadvantaged socioeconomic groups and people who do not typically use health services.(122) A study by Cardarelli et al. (2017) used focus groups with community members who met LDCT selection criteria to inform selection of media, venues and methods for the campaign, as well as consumer participants on campaign advisory boards for the development of campaign materials.[147] In another study, Springer et al. contracted a marketing agency to work with advice from the prevention and control services to inform communities about LDCT screening.(157) A study by Jessup et al. that targeted caregivers aged 18 years and older (e.g. spouses, adult children) acknowledged that caregivers and family members may have an influence over healthcare decisions and participant engagement.(156) An Italian study by Veronesi et al. used direct telephoning to families as a way of identifying high-risk individuals; however, it was acknowledged that the costs were probably too high to be a widespread recruitment method.(124)

Increasingly, social media is used to access and influence health behaviours of eligible individuals in the community who may not have current contact with health services. Social media may be more cost-effective and have a broader reach than traditional media. Studies using social media and search engine outreach have demonstrated digital campaign click-through rates higher than the healthcare industry and increased visits to institutional web pages about LDCT screening.(156, 157) These campaigns typically portray messages of mortality benefit and eligibility criteria, and link individuals to websites that provide screening information and resources. The study by Jessup noted that the highest click-through rates resulted from content that referenced signs of lung cancer and the benefits of early detection.(156)

Public health campaigns need to be sustained for several years to increase LDCT screening rates to a similar level seen with the ongoing campaigns for breast, cervical and colorectal cancer screening.(157) Further research is also warranted to ascertain the impact of population-level interventions on LDCT screening uptake.

Shared decision-making

Shared decision making (SDM) is an essential component of LDCT screening programs. In the US setting, engagement in SDM is one of six program recommendations outlined by the USPSTF and was mandated as a prerequisite for Centers for Medicare & Medicaid Services (CMS) reimbursement to the LDCT screening facility.(84) The SDM consultation must include the use of one or more decision aids about: eligibility assessment, the benefits and harms of LDCT screening, the screening continuum and the value of smoking cessation (for current smokers) prior to screening taking place.(84, 146, 122, 158) The consultation must be led by a credentialled provider such as a physician, nurse practitioner or clinical nurse specialist(84) and is particularly important when follow-up testing is warranted.(146, 158) In practice, approaches to SDM vary and include discussion facilitated by the referring provider, discussion deferred to the coordinator(114) and the mailout of decision aids, either with or without a phone call to further discuss materials.(112, 119, 108)

Despite mandatory SDM, evidence as to its effectiveness or routine implementation is lacking. The Evidence Check located one RCT that evaluated the impact of a novel information film on SDM for individuals considering participation in a LDCT screening program. This study was nested in a large British trial, the Lung Screen Uptake Trial (LSUT), which has not yet reported main outcomes; however, a protocol paper was identified by the search strategy.(80) The study participants (n=229) were randomised to receive both the film and an information booklet, or the booklet alone (control); objective and subjective knowledge measures were recorded prior to and after intervention delivery. The intervention group had greater 2.16 points (standard deviation [SD] 1.8 compared with 1.84 points (SD 1.9) in the control group (β coefficient 0.62; confidence interval, 0.17–1.08; P=0.007).(80) More participants watched the entire film than read the entire booklet (100% vs. 62%, $p<0.001$) While there were no differences in final screening participation rates between the two groups, the film reduced decisional conflict. The film had a greater impact than the

booklet about two topics in particular: understanding radiation exposure and that an 'unclear' (indeterminate) finding carries a low risk of malignancy.(80) This type of film intervention provides an alternative education method for people with low levels of health literacy and could be cost-effective (no data about cost were provided).

A comprehensive (non-systematic) review of SDM by Lowenstein et al. highlights the poor quality of SDM consultations in the US setting, including significant variation in provision across screening centres and providers, and that many healthcare providers lack the necessary skills to facilitate a discussion.(158) These findings are reinforced by evaluation studies identified for the Evidence Check(113, 120), including a qualitative content analysis study by Brenner et al. that evaluated clinicians' performance in SDM encounters.(159) This study analysed a small sample (n=14) of recorded physician or pulmonary specialist and patient encounters about initiating LDCT screening. It used a validated scale designed to measure the extent to which clinicians involve patients in decisions within consultations, and found the quality of SDM to be poor, the explanation of potential harms of screening to be virtually non-existent, time spent discussing LDCT screening to be minimal, and *"no evidence that decision aids were used"*.(159)

Decision aids have been shown to significantly improve patient knowledge regarding the benefits and potential harms of LDCT screening. Multiple patient decision aids for LDCT screening, including brochures and interactive web-based aids and prediction tools are available.(119, 158) A study by Fabbrini et al. comparing direct invitation (mailout of education decision aid, plus phone call) and usual care (mailed letters only) suggested the decision aid raised awareness of potential harms in the direct invitation group. However, the program evaluation noted resource constraints associated with SDM via phone calls facilitated by the program manager; subsequently the phone calls were dropped in favour of invitation by mailed letters only.(108) The qualitative study of three centres by Gesthalter et al. noted that one centre tested the use of information sessions, but the strategy was ultimately cancelled due to low attendance.(114)

Web-based decision-making aids have been evaluated as highly acceptable by potential LCDT screening participants; Lau et al. used a personalised decision-making approach in developing a web-based decision aid that provides individual estimates of lung cancer risk, screening benefits and harms.(160) Risk calculators may also be used to assist with SDM, with risk prediction results having a role in discussions. Visual depictions and icon arrays have been used in decision-making aids to convey to potential participants complex information such as the magnitude of benefits and harms.(158)

Education of healthcare providers

The education of healthcare providers, particularly those in primary care, is a core component of implementing a high-quality LDCT screening program.(103, 158) Primary care providers (GPs) have broad access to potential participants in their caseload, often with intimate knowledge of their patients' overall health and an existing positive relationship to facilitate SDM. However, GPs are not necessarily knowledgeable about LDCT screening effectiveness, benefits, harms, or how best to communicate eligibility.(94, 114, 120) There is very little evidence about Australian GPs' knowledge of LDCT screening beyond a survey conducted by Manners et al. into current practices in Western Australia.(92) This small survey of 93 GPs identified that opportunistic screening of individuals was taking place, but practices were not based on evidence.

There is little evidence about the most effective strategies to engage GPs in referring high-risk patients to LDCT screening, including how best to educate providers about eligibility criteria and screening requirements.(118) The importance of educating providers cannot be underestimated; the previously described retrospective cohort analysis by Li showed patient uptake of LDCT screening was more likely if the patient had seen his or her own GP than not (8.5% vs. 4.7%, p<.0001).(155)

The use of physician-led(102, 114) and LDCT screening coordinator-led(112) educational sessions that detail the LDCT examination procedure and provide ongoing feedback about screening outcomes have been reported in US program evaluations. Other outreach education strategies include grand rounds(102, 103), meetings with directors of affiliated primary care clinics(122), medical staff meetings and seminars(107), webinars(103) and information dissemination through health services intranets and web pages.(122) Successful programs include early outreach to GPs, including educational sessions that emphasise LDCT screening as a tool to improve quality of care and outcomes for individuals at high risk for lung cancer.(102) However, there are no RCTs in this area to make definitive recommendations as to whether any strategy is more effective than another, nor how these strategies might influence screening uptake.

Across US program evaluations there were some examples of electronic record tools that have been used to supplement GP education, with EMR clinical reminders that prompt GPs to discuss eligibility and engage in SMD(114, 111) using a 'best practice alert' function. These pop-up alerts prompt a GP about clinical topics such as eligibility for preventive care activities. This could increase awareness and referrals among providers but has not been widely evaluated.

3. Delivery of a screening program

Planning phase

The planning (or pre-implementation) phase of an LDCT screening program outlines program governance and the significant human, technological and infrastructure requirements that are needed to deliver effective LDCT screening. These include the personnel (human effort) required to coordinate a screening program across primary, secondary and tertiary health services and community settings.

The planning components vary across high-income countries. In the UK, the NHS has released a standard protocol for pilot projects to ensure a 'consistent and equitable approach' to service provision.(99) This includes that sufficient capacity and infrastructure be in place, including community facilities for installing mobile CT scanning units; and primary care facilities to support eligibility assessment, scanning capacity, radiological reporting, clinical service for work-up and treatment of referred participants, smoking cessation support and advice, and administrative support to facilitate data collection, collation and submission to a centralised register.(99) The responsibilities of key clinical roles and responsibilities are also detailed and include a steering group to oversee program planning and delivery.

In the US, LDCT screening programs are underpinned by the USPSTF and CMS requirements and by protocols developed by relevant professional bodies, such as the American College of Radiologists. An implementation guide from the American Thoracic Society (ATS) and American Lung Association provides a pragmatic guide and toolkit about how to 'design, implement and conduct' an LDCT screening program.(98) Evidence from the US program evaluations is useful for eliciting descriptions about how infrastructure can be developed through EHRs and data management systems to streamline processes. The most detailed example is contained in a supplementary file of the Kinsinger et al. VHA evaluation, which details resources that were created to facilitate program planning and implementation.(161) These are an implementation guide, with recommended approaches, resources, tools and an evaluation plan; a patient information tracking system; patient education materials (about LDCT screening and decision aids); three forms of electronic clinical reminders (tobacco pack-year, provider initial screen and repeat screen); a template and database system; guidelines for radiology (nodule) management; a coordinator and radiologists' training program; and a quality assurance program.

Similar resources are reported for single-site evaluations. The two best examples are visit-based (EHR) reminders to prompt physicians to consider patient eligibility and offer screening (where appropriate) and how to conduct an SDM consultation about benefits and harms(106); and examination orders for, and

internal radiology protocols for, LDCT performance based on national guidelines and standardised reporting templates including protocols for guideline-based pulmonary nodule evaluation by VHA.(114)

Ensuring safe delivery of an LDCT screening program

LDCT screening trial policies, protocols and program evaluations provide guiding information for the safe delivery of an LDCT program overall and specific to the actual examination.(97, 101, 93-95, 100, 96, 99, 98) Safe delivery of a program includes formalised clinical governance.(99) The British standard protocol and US guidelines detail the essential program requirements, including CT equipment and volumetry software requirements; CT image acquisition protocols; exposure to radiation factors; and CT image reconstruction and interpretation.(99) Guidelines for the training and accreditation of radiologists in the interpretation of scan results and using nodule management protocols are also documented.(162)

Multidisciplinary team engagement

Multidisciplinary team (MDT) engagement is essential to all program delivery models of LDCT screening. The roles and responsibilities of the MDT are typically based on consensus statements rather than evidence.(98) Disciplines involved include respiratory (pulmonary) medicine, radiology, thoracic surgery, radiation oncology, medical oncology, nursing, internal medicine and pathology. Other related disciplines, including primary and community care, allied health, information technology, statistics, marketing and administration, are less frequently mentioned in evaluation studies. MDTs appear to be central to ensuring logistical and operational issues are maintained, as well as generating topics for research and data quality.

Several of the program evaluation studies noted that MDTs hold weekly meetings to review indeterminate findings, plan treatment and refer patients with other diagnoses to other specialities.(104, 117, 9, 118, 111) A qualitative study by Gesthalter et al. of 29 staff across three LDCT screening centres identified strong supports for MDT approaches in implementation including routine meetings for the evaluation of and generation of recommendations for concerning results.(114) The authors note that regular MDT collaboration can reduce communication breakdown, such as lack of clarity about task ownership and allocation of responsibilities.

Role of coordinators

The coordinator role in the MDT team has been described as an essential part of quality LDCT screening programs, being pivotal to program development, implementation, maintenance and surveillance.(117) Two evaluation studies provide descriptive accounts of the nurse coordinator or navigator role (often fulfilled at the credentialled nurse practitioner level)(148, 110); however, there are no formal data-driven evaluations. The role can involve the daily activities of patient care coordination, including participant identification, education, confirmation of eligibility, SDM about screening participation, scheduling of LDCT scans, notification of results and follow-up care. Screening coordinators may also serve as the MDT intermediary that facilitates communication and negotiates workflow.(114) The LHC mobile screening van pilot study was nurse-led, although evaluation data about the coordination role has not been reported to date.(75)

Implementation of the screening program

The implementation of an LDCT screening program encompasses the components described in all preceding sections, as well as considerations about the reading and interpretation of scan results by radiologists and patient–provider communication.(97, 101, 93-95, 100, 96, 99, 98) Radiological guidelines about the diagnostic work-up of LDCT scans, including reading, interpretation and standardisation of reporting results, is a detailed body of literature in its own right that could not be fully scoped for the Evidence Check. Silva et al. note *"there has been a remarkable evolution"* in the definition of a positive test result over the past decade.(163) The systematic review by Snowsill provides details about radiological reading within LDCT screening trials(19) and the policy statements and guidelines provide thorough guidance about implementation in practice.(99, 162) This includes the use of clinical pathways that

streamline the reporting of results to the patient and to a centralised register for recording of essential data and to enable follow-up for referral to treating medical specialists (for positive scans) and organising repeat scans.(95)

With regards to communication, policy statements provide guidance about two issues. The first is communication of test results to the patient. The NHS protocol provides detailed guidance about how the LDCT scan results should be reported to patients via letter or telephone (with little mention about the use of face-to-face consultations); the guidance advises immediate action in the case of both positive findings and indeterminate results and the follow-up that is required.(99) Across the program evaluation studies, there was no mention of communicating test results to patients, nor are there any randomised trials that assess how best to deliver the news of a positive scan to the patient. Furthermore, there is sparse literature about uptake of invitations for repeat scans after an indeterminate result (e.g. in the NELSON trial, this was at six-to-eight weeks or after 12 months, depending on the nodule size and screening round.(19) The LHC second-round data notes that of the 71 participants with an indeterminate result, 69 (97%) attended for a three-month repeat scan, of which 6 (8.7%) were positive and 63 (91.3%) were negative.

The second issue is the communication of test results to primary care physicians. As with communication to the patient, the Evidence Check did not identify any studies about how to optimise the timely delivery of test results from the LDCT screening program to the GP, nor did any of the evaluation studies report data.

A final point in this section is the referral to treatment for participants with a positive scan. Clinical pathways manage the process of referring patients with a positive scan to the appropriate specialists (typically respiratory physicians or thoracic surgeons) within a designated cancer service. Given that most (60%–80%) screen-detected lung cancers will be Stage I or II, curative surgery with or without radiation therapy is the likely active treatment patients will undergo. Screening guidelines contain only limited information about participants exiting the LDCT screening program and following a defined pathway to ensure the timely commencement of treatment.

Maintenance phase

The CHEST/ATS implementation policy considers that the maintenance phase includes data collection and continued patient and provider education.(94) Maintenance includes patient communication reminders about follow-up adherence for repeat scans; this requires efficient systems to be in place including the earlier-mentioned registries and coordinators to contact participants. The British standard protocol includes brief guidance about data management across items of collection, handling, input, consent and maintaining the dataset.(99)

Quality assurance (QA) programs are required for monitoring patient outcomes and safety and to facilitate benchmarking across LDCT screening programs. Several guidelines or policy statements address quality assurance from the perspective of radiology monitoring.(162) The VHA evaluation by Kinsinger et al. describes quality assurance activities in the supplementary file(161) for a random sample of 35 patients, as well as second readings of 63 radiology scans. Quality assurance is briefly mentioned in European policy statements(101) and in the accreditation of LDCT screening facilities in the US setting.(162)

4. Data reporting and research

Data reporting from a centralised register requires ongoing infrastructure to enable improvements. While requirements for data reporting are addressed in earlier sections, it should be noted that the Evidence Check found no information about the routine evaluation of LDCT screening programs through mechanisms such as audit and feedback. Several LDCT screening experts call for the need to build new research initiatives into ongoing trials and real-world programs.

5. Smoking cessation as a component of LDCT programs

The Evidence Check identified two systematic reviews that specifically addressed the topic of combining smoking cessation interventions with LDCT lung screening: one by Iaccarino et al. (2019) and one by Pineiro et al. (2016).(31, 25) The Iaccarino et al. review is the most recent, having searched the literature published between 1950 and May 2018. It included nine comparative studies, five of which were RCTs, and one pilot RCT from Australia by Marshall et al. (which is part of QLCSS).(164, 87, 89, 165) The authors determined that there was insufficient data to conduct a meta-analysis due to a limited number of studies (several of which were rated as poor-to-fair quality), as well as inconsistencies in intervention designs. The review concluded that the optimal strategy for smoking cessation in patients undergoing LDCT screening was unclear.(25)

The evidence base about the inclusion of smoking cessation as a formal component of LDCT screening is rapidly evolving. There is widespread agreement that LDCT screening attendance presents a 'teachable moment' for cessation advice, especially among people who receive a positive scan result.(89, 67, 9) Inclusion of a smoking cessation program component will also improve LDCT screening cost-effectiveness.(89) Studies suggest that at least 50% of individuals undergoing LDCT screening will be current smokers.(9) Further, evidence indicates that LDCT screening does not falsely reassure smokers or reduce their motivation to stop smoking.(67) However, one study of current smokers, by Zeliadt, found offering LDCT screening may negatively influence cessation efforts.(166)

Evidence from LDCT screening trials indicates that combining smoking cessation intervention with LDCT screening has a similar effect in terms of quit rates when compared with controls, leading to the suggestion that participation in a screening trial, regardless of randomisation, may increase smoking abstinence.(167) The overall quit rate among LDCT screening participants has been reported to be as high as 14%–22%, in contrast to the 3%–7% quit rates expected in general adult populations.(25) Higher quit rates among screening participants are attributed to the fact that those who volunteer to participate in LDCT screening are more motivated to stop smoking than the general population.(167) Smoking cessation is an area of significant research investment and in the next section the evidence is reviewed for research studies from high-income countries.

Australia

The QLCSS compared a single session of tailored face-to-face counselling on the day of a screening CT scan, coupled with audio and printed cessation information, with a control group who received printed quit materials and Quitline contact details only.(89) At one year, self-reported quit rates were n=4 (14.3%) in the intervention group and n=5 (18.5%) in the control group. The combined 12-month quit rate of 16.4% was consistent with other reports. This small-scale study intervention involved physician-delivered counselling, which raised questions about its feasibility and cost-effectiveness in high-throughput screening programs. The study showed it was feasible to deliver smoking cessation interventions during a LDCT screening visit but the authors acknowledged that effective high-throughput smoking interventions that can be easily integrated with CT screening remain unmet. Furthermore, physician-led counselling was acknowledged as unlikely to be scalable or cost-effective in an LDCT program and the study recommended that smoking cessation counselling should be nurse-led.

Europe

The NELSON trial found combining low-dose CT screening with smoking cessation advice led to sustained abstinence.(87) A subgroup of male current smokers enrolled in the trial were randomised to receive a standard brochure or a tailoring questionnaire necessary to provide individualised smoking cessation information. Those who received the tailoring questionnaire were asked to complete and return the questionnaire before they received the tailored smoking cessation advice. The intervention showed an advantage compared with a standard self-help brochure on prolonged smoking abstinence after two years of follow-up. In fact, many participants did not remember that they had received the intervention, indicating that a single tailored intervention during screening is not sufficient to have long-term impact. The overall quit rate in LDCT screening participants (14%) was higher than expected from the quit rates in the general adult population (3%–7%).(87)

The Danish Lung Cancer Screening Trial (DLCST) evaluated the effect on smoking habits of screening with LDCT at one-year follow-up.(167) Trial participants received annual nurse-led counselling for less than five minutes, regardless of LDCT or control group allocation. Results indicated no difference in quit rates between the LDCT (11.9%) and control groups (11.8%), nor significant difference in smoking relapse rates between the CT (10.0%) and control groups (10.5%). The overall quit rate of 6% was higher than the usual quit rate for smokers in the general population (4%).

UK

The pilot trial of LDCT screening, known as UKLS, identified a net cessation rate of 11% in the short term and 22% at up to two-year follow-up, which are both higher than the background cessation rate of 4% in the general British population.(67) Smoking cessation rates were 8% (control n=36/479) versus 14% (intervention n=75/527) at 12 months and 21% (control n=79/377) versus 24% (intervention n=115/488) at two years, suggesting the odds of quitting were higher among screened participants compared with controls, and that intervention participants who needed additional clinical investigation were more likely to quit than those in the control group or those who received a negative screening result. The authors concluded that a positive lung screening result may provide an additional stimulus for quitting over and above that of screening participation alone.

US

Within the NLST, the combination of LDCT screening and smoking abstinence resulted in the maximum reduction in lung cancer mortality.(66) A pilot RCT by Taylor et al. evaluated a telephone-based smoking cessation intervention that reported biochemically verified quit rates of 17.4% (n=8) for the intervention (telephone counselling) group, compared with 4.3% (n=2) in the control (usual care group), suggesting preliminary evidence that telephone-based cessation counselling is feasible and efficacious in the LDCT setting.(165) A pilot study by Ferketich et al. examined the feasibility of combining a tobacco dependence treatment with LDCT screening, in which volunteer participants (n=18) received a treatment protocol consisting of nurse-delivered telephone counselling, a pharmacological prescription and medical oncologist advice; these were delivered either prior to or following LDCT screening. Results suggest it may be better to deliver treatment before the screening test. Both these studies had small sample sizes and the authors acknowledge that RCTs with a larger sample size are needed to confirm findings.[166]

Many LDCT screening sites have indicated that there are significant implementation barriers to the delivery of tobacco cessation care.(118) These include lack of patient interest, lack of staff training and complexities of navigating reimbursement for smoking cessation services. Other barriers were identified by Ostroff et al. through a brief online survey with a purposive national sample of site coordinators from 93 LDCT screening sites.(90) The study sought to describe organisational priority, current practice patterns and barriers to the delivery of evidence-based tobacco use treatment within LDCT screening sites. The findings similarly

identified that patients had poor motivation and resistance to cessation advice and treatment, staff training was poor and reimbursement (prior to the CMS mandate) was a significant barrier to delivering smoking cessation with the programs.

In response to the small-scale research and barriers, the US Government has provided specific funding support for large RCTs through the SCALE (Smoking Cessation within the Context of Lung Cancer Screening) Collaboration.(9) This initiative comprises eight clinical trials (seven funded by the National Cancer Institute and one by the Veterans Health Administration). SCALE funding supports comparative studies that test smoking interventions for patients undergoing LDCT screening and contributes to the evidence base of effective interventions delivered in this setting. These RCTs are *"testing various permutations of smoking cessation intervention strategies of different intensities (e.g. Quitline, cessation medications and medication sampling, integrated care, training toolkits, digital resources such as web-based programs and text messaging, gain vs. loss message framing)"* (p.174) The authors acknowledge that further research is needed to *"determine effective, scalable clinical workflow regarding where, when, how, and by whom smoking cessation treatment should be delivered"* (p.174).

Question 4: What is the cost-effectiveness of lung cancer screening programs (include studies of cost–utility)?

Assessing the value, or cost-effectiveness, of LDCT screening is a complex interplay of factors, including data on effectiveness and costs, and institutional context. A key input is data on the effectiveness of potential and current screening programs (as described in the evidence summaries presented in Questions 1 and 2) with respect to case detection, and the likely outcomes of treating those cases sooner (in the presence of LDCT) as opposed to later (in the absence of LDCT). In many instances, those outcomes are expressed as the combined impact of screening detection on the mortality and morbidity associated with lung cancer through the use of the quality adjusted life year (QALY). Outcomes are coupled with estimates of resource use (costs) associated with the delivery of screening and, importantly, for the delivery of care associated with the confirmation, treatment and follow-up of lung cancer cases. Given the complex interplay associated with estimating both short- and long-term efficacy and resource use, particularly over the range of possible screening regimens available (see Question 1), assessments of cost-effectiveness in this field have adopted detailed disease modelling approaches, often focused on the use of microsimulation modelling that allows individual behaviour to be simulated through a detection and treatment pathway. The outputs from such analyses require careful interpretation in that they are context-dependent, reflecting the healthcare system and related institutional arrangements, and statements of 'cost-effective' practice rely on a predetermined threshold (willingness-to-pay) of what would be considered cost-effective (which may or may not reflect the local context).

The Evidence Check identified two recent systematic reviews that capture the complexity of assessing cost-effectiveness for LDCT of studies published before 1 January 2017, by Raymakers et al. and Snowsill et al.(28, 19) Our search strategy also found 13 original articles published since the Snowsill review was completed. Six studies used microsimulation models to predict likely outcomes of LDCT screening, including benefits and harms and the downstream cost of treatment. Seven studies used a range of methods to estimate cost-effectiveness. Twelve of the 13 studies are summarised in Table 11; the exception is a discrete choice experiment by Norman et al., which is summarised as a narrative only as it does not provide cost estimates but instead captures those attributes that may drive future costs.[177]

The two systematic reviews are summarised as follows. In an analysis of 13 studies, Raymakers et al.[28] found cost-effectiveness estimates for LDCT varied substantially between studies according to the metric applied; some studies apply life-years gained (LYG) and others QALYs, with one study using Disability Adjusted Life Years, or DALYs, as the point estimates. The authors noted that in studies that reported the incremental cost-effectiveness ratios (ICER) as the cost per LYG, the ICER ranged from US$8441 to US$201,847 per LYG

for one-time screening, and US$18,452 to US$66,480 for repeated screening. The key drivers of cost-effectiveness were *"particularly sensitive to the prevalence of lung cancer, the cost of the LDCT screening test, the proportion of lung cancer detected as localised disease, and lead time bias. In addition, for those studies that included a smoking cessation program, the model results were particularly sensitive to the characteristics of this program."* (p.414)

The systematic review by Snowsill et al.[19] found *"markedly variable estimates of the cost-effectiveness of screening"* across 19 identified studies of variable quality, and with ICERs ranging from low thousands of US dollars per QALY to in excess of US$100,000 per QALY. The authors performed their own modelling scenarios for the National Health Service in the British setting (based on the UKLS trial) and estimated that the most cost-effective strategy for the UK would be a single screen for individuals aged 60–75 years with at least a 3% risk of lung cancer (summarised as S–60–75–3%). This strategy was associated with an ICER of approximately £28,000 per QALY and was considered cost-effective under the scenario, with a cost-effectiveness threshold of £30,000 per QALY. Screening was predicted to improve the stage distribution and survival of lung cancer, but also to result in overdiagnosis. The results of the cost-effectiveness analysis were particularly sensitive to the natural history of lung cancer (lung cancer survival, other-cause mortality, pre-clinical lung cancer incidence) and the cost of LDCT screening and treatment (p.105). Scenario analyses showed cost-effectiveness was improved if there was no negative impact on HRQoL from false positive or indeterminate results and applying a lower discount rate to health outcomes (p.113).

As with the Snowsill findings, studies analysed for the Evidence Check observed wide variation in cost-effectiveness scenarios across eight of the 13 studies that were included in a summary of base-case cost-effectiveness (see Figure 3). The studies that found LDCT screening can be cost-effective were by: Hinde et al., which analysed actual costs of LHC mobile screening vans in the UK(168); Kumar et al., which quantified the value of risk-targeted selection for LDCT screening compared with NLST eligibility criteria for the US population(169); Yang et al., which analysed the cost-effectiveness of LDCT screening in Taiwan(170); and, finally, Treskova et al., a microsimulation modelling study in a population-based setting in Germany.[71]

The study by Treskova et al. is one of the few studies to include modelling scenarios similar to the NELSON trial.(71) It aimed to investigate the effects of the eligibility criteria and nodule management on the benefits and harms of screening. The base case was five-year LDCT screening and 76 scenarios were tested based on age (at starting and quitting smoking), smoking history (years/time since quit) and nodule status (using NLST- and NELSON-like nodule management protocols). Cost-effectiveness was represented by average and incremental cost per LYG and averted lung cancer deaths. The most cost-effective scenario yielded an ICER of €16,754/LYG; this strategy is summarised as 55–74–40–10 (55–74 year age range, 40 pack-years and 10 years since quitting), with the NELSON-like nodule management protocol, with assessment of volume-doubling time of three months after the initial screening as a sole predictor of malignancy).

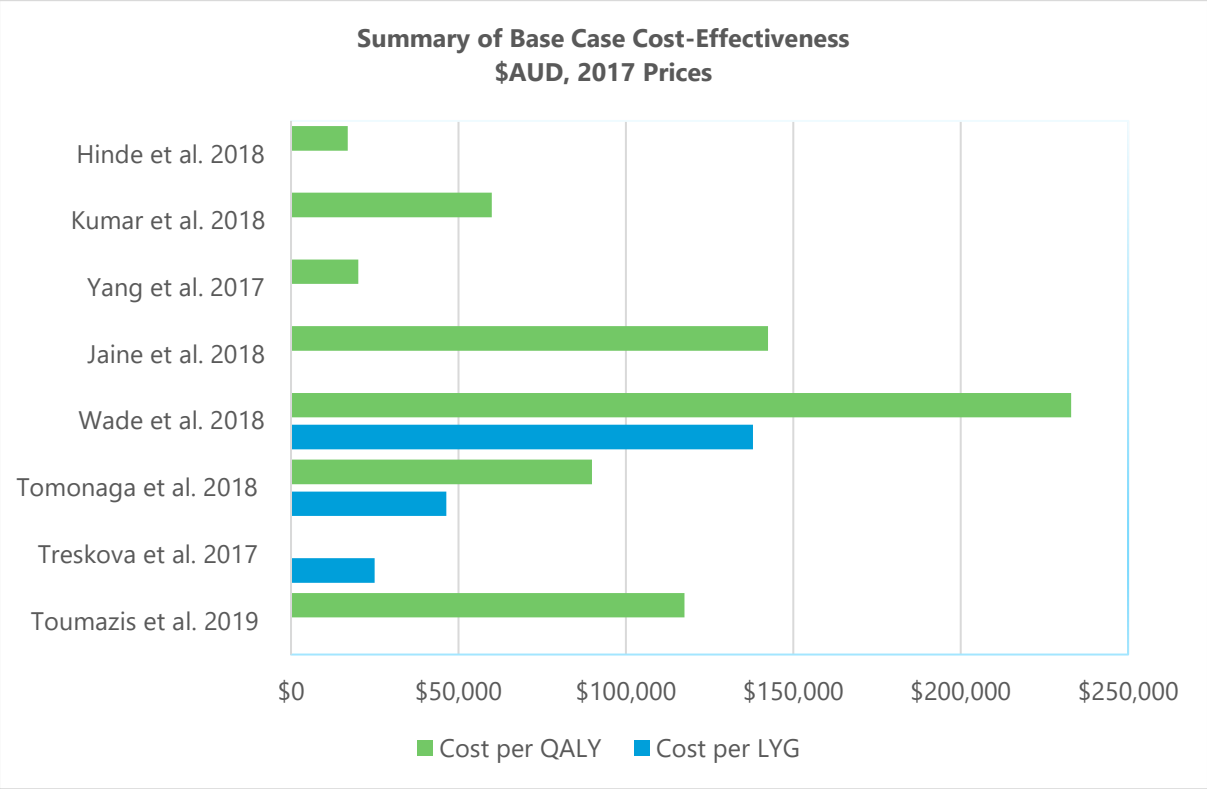


Figure 3: Summary of the base case cost-effectiveness for eight LDCT screening studies, converted into 2017 Australian dollars.

Studies that exceeded a nominal threshold considered to cost-effective, i.e. in excess of $100,000 per QALY or LYG, include: a macrosimulation modelling study by Jaine et al. for the New Zealand population[143], a microsimulation study by Tomonaga et al.(171) for the Swiss population, Toumazis et al.(172), and Wade et al.[173] in Australia. Of these studies, Wade et al. is of particular interest to this Evidence Check due to the Australian context, having applied Australian population-based survival rates and cost estimates to NLST data over a 10-year time horizon. The authors estimated a cost of AU$233,000 per QALY gained and AU$138,000 per LYG, well above what typically would be considered cost-effective locally.(173) The ICER was more favourable when the impact of LDCT screening on all-cause mortality was considered, with AU$157,000/QALY gained (using an indicative willingness-to-pay threshold of AU$30–$50K/QALY). The authors note that the results were sensitive to the inclusion of all-cause mortality, the quality of life effects associated with false positives and the costs of following up false positives. They also highlight the importance of the proportion of cases detected at early stage disease to the estimates of cost-effectiveness, and that case detection is in turn influenced by the characteristics and number of those who participate in cancer screening programs.

Toumazis et al.(172) assessed the cost-effectiveness of LDCT screening after incorporating the Lung-RADS guidelines to manage indeterminate findings for the US population. This model considered both annual and biennial screening, screening start–stop scenarios and varied smoking exposures. A cost–utility analysis (cost per QALY) was undertaken and used a base-case analysis that assumed a 4% short-term disutility results in only biennial strategies being cost-effective at a threshold of US$100,000/QALY. The most cost-effective scenario yielded an ICER of US$92,561 for the strategy B–50–70–40–10 (starting age of 50 and stopping age of 70 years, 40 pack-years and 10 years since quitting) producing the highest QALY gain. The authors conclude that with a stated threshold of at least US$100,000 per QALY (as the willingness-to-pay threshold),

there are some annual strategies that are cost-effective assuming no disutility of indeterminate findings and only biennial strategies (assuming a 4% disutility).

The three remaining studies that were identified provide information of less relevance to the broader context of the Evidence Check review.(174, 175, 73) The study by Chung et al.[174] conducted a profitability analysis of an LDCT screening program in an underserved community in the south-eastern US state of Georgia. Huo et al.[74] examined complication rates and the downstream medical costs associated with invasive diagnostic procedures following identification of lung abnormalities in LDCT screening, using a US medical insurance claims database. The study by Gareen et al.[175] sought to determine comparative costs across the two arms of the NLST trial (LDCT and CXR), and the impact of significant incidental findings (SIFs) using linked data obtained through linkage with Medicare administrative billing data.

This Evidence Check identified two additional studies relevant to LDCT lung cancer screening program cost considerations in the Australian context: Marshall (2019)(176) and Norman (2019).[177] The study by Marshall et al. uses resource use data from the QLCSS cohort trial (as described in Q1) and the NLST trial data to estimate the costs associated with LDCT screening. Healthcare status and usage for study participants was collected for five years; participants had up to three scans n=256 (R1); n=239 (R2) and 233 (R3). The main outcome measures were rates of lung cancer and individual healthcare resource use derived from multiple data sources adjusted to 2018 Australian Medicare Benefits Schedule (MBS) values. Twelve participants were diagnosed with lung cancer during screening and two during follow-up scans. Costs for all treatments (surgery, chemotherapy, radiation therapy and palliative care) were collected and descriptive statistics were presented due to the small numbers of cohort participants. The authors conclude:

> *"In summary, our cost data appear similar to NLST results and suggest that screening could limit treatment cost and improve outcomes. However, the NLST and QLCSS trial designs have been superseded by targeted recruitment using multivariable risk estimation, better stratification of nodule risk using volumetric measurement and/or probabilistic risk assessment. Refinements in screening delivery have the potential to moderate costs by reducing the screened population and driving down false-positive scan rates. At the same time, the cost of treating advanced lung cancer will increase as more novel therapies are developed and deployed. We believe these factors will swing the balance of cost effectiveness in favour of screening: detection of early stage, resectable lung cancer not only represents the best chance of cure for patients, but will also represent good value for money."*

Access to data as reported by Marshall et al. is critical in assessing the long-term cost-effectiveness of LDCT since this must include the costs of treatment of cases detected (and not be limited to the cost per case detected).(176) The recent uptake of immunotherapies and targeted therapies, many of which incur very high costs, must be considered in future analyses. For example, the Hinde analysis from the UK did not include these costs whereas other studies do include them.

The study by Norman et al. (in press) is a discrete choice experiment (DCE) about LDCT screening in the Australian setting. The DCE is a survey method that present participants with a series of hypothetical but realistic questions and, based on their choices, analyses which aspects of the decision context matter most. It follows a health economics approach that characterises how people make choices that are driven by a set of dimensions (known as 'attributes') at particular levels. In the case of LDCT screening, DCEs can provide significant data to inform the estimates of uptake. In this study, an online survey was completed by 503 Australians aged 50–80 years with a smoking history. The study aim was to identify the aspects of LDCT screening that were relatively more or less attractive to individuals likely to be targeted for screening, with screening options described by type of scan; radiation dose; distance from home; time at the scan location; speed of receiving results; hospital versus non-hospital testing; the use of the public- or private-sector providers; and the cost to the individual. The survey found that for high-risk individuals, providing a fast and

convenient test was of particular importance, as was receiving results in a timely way. Participants in the high-risk group appeared less willing to travel significant distances and would spend less time at the testing location than people at lower risk.

The findings of this DCE provide crucial data about the likely estimates of uptake of LDCT screening. As identified in the existing reviews of cost-effectiveness(28, 19), ICERs in this setting are sensitive to lung cancer detection/natural history and costs of LDCT. The former is not only dependent on the population selected to participate in screening, but also on the uptake of those in that population within a screening program. As identified by Wade et al., lung cancer detection and stage are influenced by who participates in screening.(173) Similarly, as shown in Snowsill (p108), altering the uptake rate influences what is considered a cost-effective strategy.[19] Set-up costs associated with LDCT (including education and recruitment) will increase on an average participant basis as participant uptake numbers decrease, with an impact on cost-effectiveness.

Other factors that may drive the cost-effectiveness of LDCT screening are smoking rates and smoking intensity. A study by Cancer Council NSW is researching significant questions about smoking habits in the Australian population as part of the Lung Cancer Pathways project(177), which will review smoking initiation, duration and intensity (based on historical data from national and state-based health surveys). The Pathways project will provide new insights into how such factors impact on cost-effectiveness analyses when compared with European countries. We note that other factors, such as population size and geographical distribution of the population and of availability of tobacco, may also influence cost but are not addressed in the literature identified for the Evidence Check.

In terms of quality assessment of modelling studies, we found microsimulation studies were generally of high quality and studies using other designs were generally of moderate quality. It should be noted that the CHEERS scale is not typically scored but a brief coding explanation was used based on expert advice.

Gap analysis

There is a large and accessible body of evidence as to the effectiveness (Q1) and harms (Q2) of LDCT screening for lung cancer. Evidence relating to the program components required to implement an effective LDCT screening program (Q3) come from LDCT screening trials and program evaluations. There is a solid evidence base from carefully controlled trials about the clinical aspects of LDCT screening, nodule measurement and categorisation and interpretation of test results. The available policy documents and clinical practice guidelines provide consensus-based evidence about the design, implementation and maintenance of LDCT screening programs.

However, there are considerable gaps in knowledge that emerged from the Evidence Check analysis. The Australian Population Based Screening Framework was developed to *"inform decision-makers on the key issues to be considered when assessing potential screening programs in Australia"*.(10) The Framework criteria stipulate that a screening program must be acceptable to *"important subgroups such as target participants who are from culturally and linguistically diverse backgrounds, Aboriginal and Torres Strait Islander people, people from disadvantaged groups, and people with a disability"*.(10) The Evidence Check search highlighted that there is very little Australian data about the acceptability of LDCT screening in population groups at high risk of lung cancer. There is an urgent need for research to determine whether the Australian population would engage in a high-risk LDCT screening program and what factors would facilitate participation. The discrete choice experiment by Norman et al. provides some early indicators that screening costs, distance to travel to a screening facility and timely delivery of results(178) will be driving factors. The evidence gap extends to the lack of data about the beliefs and attitudes of the Australian community regarding LDCT screening. The stigma associated with cigarette smoking and lung cancer are likely to be strong drivers in community perceptions of LDCT screening and cannot be discounted.

The QLCSS provides feasibility data about clinical aspects of LDCT screening in Australia but does not provide evidence about potential recruitment strategies for a national high-risk LDCT screening program beyond the explicit inclusion of asbestos exposure in advertising. The ILST is underway in Australia and initial findings from a sub-study about recruitment strategies was not available for inclusion in this Evidence Check. However, when published, it will provide data about strategies for recruitment in primary care practices. The Evidence Check identified that evidence about recruitment and eligibility is limited and, despite large-scale RCTs, relatively little research has been conducted to identify the most effective strategies for persuading the high-risk population to undergo LDCT screening. In particular, the documentation of smoking history in medical records is a vital source for determining LDCT screening eligibility. It was beyond the scope of the Evidence Check to examine evidence from the tobacco control literature about the documentation of smoking history in the Australian context. While no Australian studies about the collection or accuracy of smoking history specific to LDCT screening were identified in the search strategy, the CHEST Australia trial, a randomised trial to reduce time to presentation of lung cancer symptoms in primary care by Emery et al., has tested the 'Canning tool' data extraction software to identify current and former smokers.(179, 180) Knowledge from this trial will help to address the evidence gap, although it should be anticipated that across health systems, medical records will be unreliable and incomplete regarding smoking history.

The literature covering community awareness and the education of healthcare providers and the public about LDCT screening indicates that there are significant gaps in the evidence base. In response, there is enormous scope to design and test digital health strategies to educate the public and providers about lung

cancer and a high-risk LDCT screening program. Previous research by the Evidence Check authors has highlighted significant gaps in the knowledge of lung cancer symptoms and diagnosis on the part of GPs and patients in NSW.(181) While it was beyond the scope of the Evidence Check to examine the community awareness strategies used in the existing national screening programs for breast, cervical and bowel cancer, there would undoubtedly be transferable knowledge that could help address the current gaps for LDCT screening.

The education of GPs is an essential program component of LDCT screening and the gaps in knowledge about how best to engage the primary care community would be a major research undertaking should a national LDCT screening program be pursued. This engagement would need to include the potential for SDM and smoking cessation counselling. The opportunity to use novel interventions, such as the information film about decision-making (tested under RCT conditions by Ruparel et al.[142]) could be adapted and delivered in the Australian setting, not only within an LDCT program, but also made available online for broader public education purposes.

The Evidence Check has highlighted the rapidly evolving evidence base about smoking cessation programs within the LDCT screening setting. Evidence from the QLCSS provides baseline data about how smoking cessation might be addressed in an Australian high-risk screening program. The US SCALE program of clinical trials about smoking cessation within LDCT screening programs will help to address the evidence gap about optimal strategies for delivering cessation interventions.(9) It appears nurse-led interventions are an option for a cost-effective approach to integrating cessation into LDCT programs, and the evidence gaps need to be addressed internationally.

There are also considerable gaps in evidence as to the cost-effectiveness of LDCT screening (as per Q4) in different settings, including Australia. Both the Raymakers and Snowsill systematic reviews reported considerable uncertainty about the cost-effectiveness of LDCT screening. The Evidence Review identified 13 new studies in the cost-effectiveness area that contribute to a wider evidence base about these issues. Evidence in this area is rapidly evolving and cost-effectiveness estimates will need to be updated following publication of the NELSON trial data. Further, the incorporation of costs data about targeted- and immuno-therapies will be required as these treatments become more widely available across Australia. The Evidence Check team anticipates significant research activity and investment in cost-effectiveness studies to address the existing uncertainty.

Analysis of the applicability for NSW

Overall, the findings of this Evidence Check are relevant and applicable to the NSW setting, particularly with regards to effectiveness (Q1) and harms (Q2). While the evidence as to the cost-effectiveness (Q4) of LDCT screening is unresolved, the analysis of Q3 data highlights important factors to consider regarding the acceptability and feasibility of a high-risk screening program in NSW.

There are unresolved questions about the most effective methods for delivering an LDCT screening program internationally, and these will directly inform policy review in the Australian setting.

Low uptake rates have been a significant concern reported in the US. These rates will be closely monitored, and new research will be undertaken to improve participation and incorporate smoking cessation into programs. In contrast, the British model of the Lung Health Check is highly successful and provides an attractive model to target people from lower socioeconomic communities. One factor that may contribute to this success is that access is not restricted via referral from a primary care provider. The emphasis on a holistic, nurse-led program may appeal to people from traditionally hard-to-reach groups, including long-term smokers, people living in regional, rural and remotes areas, people from CALD backgrounds and Aboriginal and Torres Strait Islanders. These groups are typically under-represented in accessing health services, have limited opportunities to engage in health planning processes and may be resistant to participating in cancer screening programs.

Evidence shows people in hard-to-reach communities have poorer lung cancer outcomes. For example, Australians from rural and remote areas have later presentation and stage at cancer diagnosis(182, 183), report limited availability of specialist oncology services(184) including restricted access to lung cancer surgery(185) and find travelling for diagnostic investigations and treatment particularly challenging.(186, 187, 181) A willingness to travel for curative lung cancer surgery for people with a positive LDCT screening result is one of many factors that will need further investigation by researchers, health economists and policy makers for the NSW/Australian context. The barriers to LDCT screening participation, including a lack of awareness (of lung cancer and of screening), access challenges, cost concerns, fear and stigma about lung cancer, lack of shared decision-making, scepticism about evidence of benefits and challenges in identifying high-risk people, have been documented across international studies.(135, 112, 131) The lack of NSW and Australian evidence about barriers and facilitators to LDCT screening should also be addressed.

Further work is required to establish the applicability of program components (Q3). A review of policy documents was out of scope; however, an analysis of how LDCT programs operate across a mixed model of public–private provision of healthcare services would benefit an understanding of how a national screening program would be designed and implemented to meet the needs of high-risk populations. Furthermore, the costs of implementing a national LDCT screening program will be influenced by the rapidly changing environment of new therapies that may extend survival, as well as stakeholder and community views about where investments should be made across prevention and treatment. It is important to reflect that data are not available about the equity issues in offering therapies to people with advanced disease; as these therapies are very expensive (and, until recently, had not been available on the Pharmaceutical Benefits Scheme) it may only be wealthier individuals who can afford them. These considerations should inform key stakeholder discussions about whether a national LDCT screening program is feasible.

Implications

The findings of this Evidence Check are highly aligned with those presented at the 2019 World Conference on Lung Cancer, the peak international conference hosted by the International Association for the Study of Lung Cancer (IASLC). The conference was held in Barcelona in early September and a key presentation from Professor Harry De Koning, principal investigator of the NELSON trial, highlighted that *"for lung cancer screening, the evidence on effectiveness, benefits that now outweigh the harms, and cost-effectiveness, is now firm"* (direct quote, slide presentation provided by Dr Emily Stone, personal communication, 8 September 2019). The Evidence Check identified that cost-effectiveness in the Australian setting is not conclusive when compared with the population-dense settings of European countries and North America. Professor De Koning announced a new European implementation study that will enrol 24,000 participants with a *"planned emphasis on recruitment strategies, co-morbidity reducing strategies, new biomarkers, and personalised screening intervals by risk"* (direct quote, personal communication, as above). This shift from effectiveness to implementation research heralds a new phase of research in LDCT screening. It is supported by a 'call for action' in the European position statement on LDCT screening(188) and by a £70 million investment in Lung Health Checks by the NHS England.(189)

The implications for Australian policy makers require careful consideration about how best to balance the gaps in evidence as outlined earlier, alongside the urgent need to address lung cancer mortality and poor survival outcomes. There is international debate about whether all-cause mortality is the most relevant end-point for cancer screening trials.(79) The NLST is the only cancer screening trial to have demonstrated a significant difference in all-cause mortality; breast and bowel cancer trials conducted several decades ago have not reported positive outcomes. Other lung cancer screening trials that met the inclusion criteria for the Evidence Check are not sufficiently powered to report on all-cause mortality alone; data must be combined across trials (as reported in Table 5). Heijnsdijk et al. note that a lung cancer screening trial that includes high-risk individuals has the 'most potential' to demonstrate a significant effect in all-cause mortality because of the high incidence and low survival rates in lung cancer, as well as tumours being generally fast-growing and having a short lead time. The long-term follow up data from the NLST about all-cause mortality did not detect a statistically significant difference at 12.3 years; however the authors note that this "should not be taken to negate the original significant finding; it is more likely related to use of the 'incorrect window' for follow-up (i.e., too long a period after screening).(190) Furthermore, long-term NLST analyses about lung-cancer specific mortality showed that LDCT screening "did not just delay lung cancer death by a few years, it also prevented it, or at least delayed it for more than a decade."[42] How evidence about all-cause mortality in trial settings is applied to the real-world delivery of screening programs is not clear. Thus, cancer-specific mortality appears to be the most relevant outcome from lung cancer screening trials.

The Evidence Check findings were primarily derived from existing systematic reviews, particularly for questions about effectiveness, harms and cost-effectiveness. There was an enormous body of available evidence to identify, extract and to succinctly summarise for the key messages. It will be necessary to reconsider the evidence following the full publication of the NELSON results and interim results from the ILST trial. A significant focus of the evidence base addresses a complex series of issues about LDCT screening trial outcomes such as risk assessment, management of indeterminate nodules, multidisciplinary team work-up, determining the best intervals for repeat screening, surgical management and dealing with the incidental findings on first and repeat screening.(188) The Evidence Check does not attempt to summarise these complexities as numerous reviews and position statements have already done so. However, the evidence base for major components of LDCT screening programs was derived from many

single-institution studies and policy documents about 'real-world' program implementation. Significant effort and investment in implementation and evaluation is required and research needs to shift to ensure that people at high risk have an opportunity to benefit from LDCT screening.

References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M. Global Cancer Observatory: Cancer Today Geneva: World Health Organisation; 2018.
2. Australian Institute of Health and Welfare. Cancer in Australia 2017. Canberra: AIHW, 2017.
3. Australian Bureau of Statistics. ABS -Statistics section Canberra: Australian Bureau of Statistics; 2019 [cited 2015 4 April 2019]. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/webpages/statistics?opendocument.
4. Scollo MM, Winstanley MH. Tobacco in Australia: facts and issues. Melbourne: Cancer Council Victoria, 2019.
5. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New England Journal of Medicine*. 2011;365(5):395-409.
6. van den Bergh KA, Essink-Bot ML, Bunge EM, Scholten ET, Prokop M, van Iersel CA, et al. Impact of computed tomography screening for lung cancer on participants in a randomized controlled trial (NELSON trial). *Cancer*. 2008;113(2):396-404.
7. Goodman A. NELSON Trial: 'Call to Action' for lung cancer CT screening of high-risk individuals. The ASCO Post; https://wwwascopostcom/issues/october-25-2018/nelson-trial/. 2018.
8. Huang KL, Wang SY, Lu WC, Chang YH, Su J, Lu YT. Effects of low-dose computed tomography on lung cancer screening: a systematic review, meta-analysis, and trial sequential analysis. *BMC Pulmonary Medicine*. 2019;19(1).
9. Joseph AM, Rothman AJ, Almirall D, Begnaud A, Chiles C, Cinciripini PM, et al. Lung cancer screening and smoking cessation clinical trials. SCALE (Smoking Cessation within the Context of Lung Cancer Screening) Collaboration. *American Journal of Respiratory Critical Care Medicine*. 2018;197(2):172-82.
10. Commonwealth Department of Health. Population Based Screening Framework. Canberra, Australia: Commonwealth Government of Australia, 2018.
11. Yang W, Qian F, Teng J, Wang H, Manegold C, Pilz LR, et al. Community-based lung cancer screening with low-dose CT in China: results of the baseline screening. *Lung Cancer*. 2018;117:20-26.
12. Lung Foundation Australia. Making lung cancer a fair fight: a blueprint for reform. Milton, QLD: Lung Foundation Australia, 2019.
13. O'Keeffe LM, Taylor G, Huxley RR, Mitchell P, Woodward M, Peters SAE. Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. *BMJ Open*. 2018;8(10):e021611.
14. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner society: glossary of terms for thoracic imaging. *Radiology*. 2008;246(3):697-722.
15. Larici AR, Farchione A, Franchi P, Ciliberto M, Cicchetti G, Calandriello L, et al. Lung nodules: size still matters. *European Respiratory Review*. 2017;26(146):170025.
16. Arenberg D. Update on screening for lung cancer. *Translational Lung Cancer Research*. 2019;8(Suppl 1):S77.
17. Veritas Health Innovation. Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation; 2019.
18. Clarivate Analytics. Endnote: Endnote X9. Boston, MA,: Clarivate Analytics; 2019.
19. Snowsill T, Yang H, Griffin E, Long L, Varley-Campbell J, Coelho H, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)*. 2018;22(69):1-276.
20. Usman Ali M, Miller J, Peirson L, Fitzpatrick-Lewis D, Kenny M, Sherifali D, et al. Screening for lung cancer: a systematic review and meta-analysis. *Preventive Medicine*. 2016;89:301-14.
21. Chandler J, Cumpston M, Thomas J, Higgins JPT, Deeks JJ, MJ. C. Introduction In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 60 (updated August 2019). www.training.cochrane.org/handbook: Cochrane Collaboration, 2019.
22. Effective Public Health Practice Project (EPHPP). Quality assessment tool for quantitative studies 2010 [1 October 2019]. Available from: https://merst.ca/wp-content/uploads/2018/02/quality-assessment-tool_2010.pdf.
23. Critical Appraisal Skills Programme. Critical Appraisal Skills Programme Qualitative Checklist 2018 [29 October 2019]. Available from: www.casp-uk.net/casp-tools-checklists/.
24. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health

Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Values in Health*. 2013;16(2):231-50.
25. Iaccarino JM, Duran C, Slatore CG, Wiener RS, Kathuria H. Combining smoking cessation interventions with LDCT lung cancer screening: a systematic review. *Preventive Medicine*. 2019;121:24-32.
26. Mazzone PJ, Silvestri GA, Patel S, Kanne JP, Kinsinger LS, Wiener RS, et al. Screening for lung cancer: CHEST guideline and expert panel report. *Chest*. 2018;153(4):954-85.
27. Wu GX, Raz DJ, Brown L, Sun V. Psychological Burden Associated With Lung Cancer Screening: A Systematic Review. *Clinical Lung Cancer*. 2016;17(5):315-24.
28. Raymakers AJN, Mayo J, Lam S, FitzGerald JM, Whitehurst DGT, Lynd LD. Cost-effectiveness analyses of lung cancer screening strategies using Low-Dose Computed Tomography: a aystematic review. *Applied Health Economics and Health Policy*. 2016;14(4):409-18.
29. Slatore CG, Sullivan DR, Pappas M, Humphrey LL. Patient-centered outcomes among lung cancer screening recipients with computed tomography: a systematic review. *Journal of Thoracic Oncology*. 2014;9(7):927-34.
30. Iaccarino JM, Duran C, Wiener RS, Kathuria H. Smoking cessation interventions in the setting of low dose computed tomography (LDCT) lung cancer screening: a systematic review. American Thoracic Society 2017 International Conference2017.
31. Pineiro B, Simmons VN, Palmer AM, Correa JB, Brandon TH. Smoking cessation interventions within the context of Low-Dose Computed Tomography lung cancer screening: a systematic review. *Lung Cancer*. 2016;98:91-98.
32. Coureau G, Salmi LR, Etard C, Sancho-Garnier H, Sauvaget C, Mathoulin-Pelissier S. Low-dose computed tomography screening for lung cancer in populations highly exposed to tobacco: a systematic methodological appraisal of published randomised controlled trials. *European Journal of Cancer*. 2016;61:146-56.
33. Li ZY, Luo L, Hu YH, Chen H, Den YK, Tang L, et al. Lung cancer screening: a systematic review of clinical practice guidelines. *International Journal of Clinical Practice*. 2016;70(1):20-30.
34. Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive services task force recommendation. *Annals of Internal Medicine*. 2013;159(6):411-20.
35. Manser R, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ, et al. Screening for lung cancer. *Cochrane Database of Systematic Reviews*. 2013(6).
36. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA - Journal of the American Medical Association*. 2012;307(22):2418-29.
37. De Koning H, Van Der Aalst C, Ten Haaf K, Oudkerk M. PL02.05 Effects of Volume CT lung cancer screening: mortality results of the NELSON randomised-controlled population based trial. *Journal of Thoracic Oncology*. 2018;13(10):S185.
38. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, et al. Lung cancer mortality reduction by LDCT screening-results from the randomized German LUSI trial. *International Journal of Cancer*. 2019.
39. Pastorino U, Silva M, Sestini S, Sabia F, Boeri M, Cantarutti A, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*. 2019;01.
40. Paci E, Puliti D, Lopes Pegna A, Picozzi G, Falaschi F, Pistelli F, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. *Thorax*. 2017;72(9):825-31.
41. National Lung Screening Trial Research Team. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. *Journal of Thoracic Oncology*. 2019.
42. Pastorino U, Sverzellati N, Sestini S, Silva M, Sabia F, Boeri M, et al. Ten-year results of the Multicentric Italian Lung Detection trial demonstrate the safety and efficacy of biennial lung cancer screening. *European Journal of Cancer*. 2019;118:142-48.
43. Infante M, Sestini S, Galeone C, Marchiano A, Lutman FR, Angeli E, et al. Lung cancer screening with low-dose spiral computed tomography: evidence from a pooled analysis of two Italian randomized trials. *European Journal of Cancer Prevention*. 2017;26(4):324-29.
44. Heuvelmans MA, Walter JE, Peters RB, Bock GH, Yousaf-Khan U, Aalst CMV, et al. Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening: the NELSON study. *Lung Cancer*. 2017;113:45-50.
45. Walter JE, Heuvelmans MA, Bock GH, Yousaf-Khan U, Groen HJM, Aalst CMV, et al. Characteristics of new solid nodules detected in incidence screening rounds of low-dose CT lung cancer screening: the NELSON study. *Thorax*. 2018;73(8):741-47.

46. Walter JE, Heuvelmans MA, de Bock GH, Yousaf-Khan U, Groen HJM, van der Aalst CM, et al. Relationship between the number of new nodules and lung cancer probability in incidence screening rounds of CT lung cancer screening: the NELSON study. *Lung Cancer*. 2018;125:103-08.
47. Marshall HM, Bowman RV, Crossin J, Lau MA, Slaughter RE, Passmore LH, et al. Queensland Lung Cancer Screening Study: rationale, design and methods. *Internal Medicine Journal*. 2013;43(2):174-82.
48. Marshall HM, Bowman RV, Ayres J, Crossin J, Lau M, Slaughter RE, et al. Lung cancer screening feasibility in Australia. *European Respiratory Journal*. 2015;45(6):1734-7.
49. Lim KP, Brims F, McWilliams A, Tammemagi M, Berg C, Marshall H, et al. The international lung screen trial: a multi-center study to evaluate LDCT screening selection criteria and nodule management. *Journal of Thoracic Oncology*. 2017;12 (11 Supplement 2):S1973.
50. Tammemagi MC. Selecting lung cancer screenees using risk prediction models- where do we go from here. *Translational Lung Cancer Research*. 2018;7(3):243-53.
51. Tammemagi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. *New England Journal of Medicine*. 2013;368(8):728-36.
52. Moyer VA, Force USPST. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*. 2014;160(5):330-8.
53. Pinsky PF, Church TR, Izmirlian G, Kramer BS. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer*. 2013;119(22):3976-83.
54. Robbins HA, Callister M, Sasieni P, Quaife SL, Cheung LC, Brennan P, et al. Benefits and harms in the National Lung Screening Trial: expected outcomes with a modern management protocol. *The Lancet Respiratory Medicine*. 2019;7(8):655-56.
55. Hewitson P, Glasziou PP, Irwig L, Towler B, E. W. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Systematic Review Database*. 2007(1. Art. No.: CD001216).
56. Lew J-B, St John DJB, Xu X-M, Greuter MJE, Caruana M, Cenin DR, et al. Long-term evaluation of benefits, harms, and cost-effectiveness of the National Bowel Cancer Screening Program in Australia: a modelling study. *The Lancet Public Health*. 2017;2(7):e331-e40.
57. Paci E. The narrow path to organized LDCT lung cancer screening programs in Europe. *Journal of Thoracic Disease*. 2018;10(7):4556-64.
58. Pastorino U, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *European Journal of Cancer Prevention*. 2012;21(3):308-15.
59. Team NLSTR. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New England Journal of Medicine*. 2011;365(5):395-409.
60. Yousaf-Khan U, van der Aalst C, de Jong PA, Heuvelmans M, Scholten E, Lammers J-W, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. *Thorax*. 2017;72(1):48.
61. Aberle DR, DeMello S, Berg CD, Black WC, Brewer B, Church TR, et al. Results of the two incidence screenings in the National Lung Screening Trial. *New England Journal of Medicine*. 2013;369(10):920-31.
62. Rota M, Pizzato M, La Vecchia C, Boffetta P. Efficacy of lung cancer screening appears to increase with prolonged intervention: results from the MILD trial and a meta-analysis. *Annals of Oncology*. 2019;30(7):1040-43.
63. Tanoue LT. Lung cancer screening. *Current Opinion in Pulmonary Medicine*. 2016;22(4):327-35.
64. Cochrane Collaboration. 'Risk of bias 2.0' tool London, United Kingdom 2018. Available from: https://methods.cochrane.org/risk-bias-20-tool.
65. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
66. Tanner NT, Kanodra NM, Gebregziabher M, Payne E, Halbert CH, Warren GW, et al. The association between smoking abstinence and mortality in the National Lung Screening Trial. *American Journal of Respiratory and Critical Care Medicine*. 2015;193(5):534-41.
67. Brain K, Carter B, Lifford KJ, Burke O, Devaraj A, Baldwin DR, et al. Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial. *Thorax*. 2017;72(10):912-18.
68. Dunn CE, Edwards A, Carter B, Field JK, Brain K, Lifford KJ. The role of screening expectations in modifying short-term psychological responses to low-dose computed tomography lung cancer screening among high-risk individuals. *Patient Education & Counseling*. 2017;100(8):1572-79.
69. Han SS, Ten Haaf K, Hazelton WD, Munshi VN, Jeon J, Erdogan SA, et al. The impact of overdiagnosis on the selection of efficient lung cancer screening strategies. *International Journal of Cancer*. 2017;140(11):2436-43.

70. Rampinelli C, De Marco P, Origgi D, Maisonneuve P, Casiraghi M, Veronesi G, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. *BMJ*. 2017;356:j347.
71. 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 Medicine*. 2017;15(1):162.
72. Caverly TJ, Cao P, Hayward RA, Meza R. Identifying patients for whom lung cancer screening is preference-sensitive a microsimulation study. *Annals of Internal Medicine*. 2018;169(1):1-9.
73. Huo J, Xu Y, Sheu T, Volk RJ, Shih YCT. Complication rates and downstream medical costs associated with invasive diagnostic procedures for lung abnormalities in the community setting. *JAMA Internal Medicine*. 2019;179(3):324-32.
74. Taghizadeh N, Tremblay A, Cressman S, Peacock S, McWilliams AM, MacEachern P, et al. Health-related quality of life and anxiety in the PAN-CAN lung cancer screening cohort. *BMJ Open*. 2019;9(1).
75. Crosbie PA, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D, et al. Second round results from the Manchester 'Lung Health Check' community-based targeted lung cancer screening pilot. *Thorax*. 2019;74(7):700-04.
76. Pinsky PF, Gierada DS, Hocking W, Patz EF, Jr., Kramer BS. National Lung Screening Trial findings by age: medicare-eligible versus under-65 population. *Annals of Internal Medicine*. 2014;161(9):627-33.
77. Frank L, Christodoulou E, Kazerooni EA. Radiation risk of lung cancer screening. *Seminars in Respiratory and Critical Care Medicine* 2013;34(6):738-47.
78. De Koning HJ. Lung cancer screening. *Journal of Thoracic Oncology*. 2012;7(6):S7.
79. Patz EF, Jr, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemägi MC, et al. Overdiagnosis in Low-Dose Computed Tomography screening for lung cancer. *JAMA Internal Medicine*. 2014;174(2):269-74.
80. Quaife SL, Ruparel M, Beeken RJ, McEwen A, Isitt J, Nolan G, et al. The Lung Screen Uptake Trial (LSUT): protocol for a randomised controlled demonstration lung cancer screening pilot testing a targeted invitation strategy for high risk and 'hard-to-reach' patients. *BMC Cancer*. 2016;16:281.
81. Quaife SL, Janes SM. Lung cancer screening: improving understanding of the psychological impact. *Thorax*. 2016;71(11):971-72.
82. Van den Bergh KA, Essink-Bot ML, Borsboom GJ, Th Scholten E, Prokop M, de Koning HJ, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). *British Journal of Cancer*. 2010;102(1):27-34.
83. Brain K, Lifford KJ, Carter B, Burke O, McRonald F, Devaraj A, et al. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. *Thorax*. 2016;71(11):996.
84. The Centers for Medicare & Medicaid Services (CMS). Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT) (CAG-00439N). Baltimore, Marylands: CMS; 2015.
85. Iaccarino JM, Duran C, Slatore CG, Wiener RS, Kathuria H. Combining smoking cessation interventions with LDCT lung cancer screening: A systematic review. *Preventive Medicine: An International Journal Devoted to Practice and Theory*. 2019;121:24-32.
86. Meltzer LR, Unrod M, Simmons VN, Brandon KO, Pineiro B, Palmer AM, et al. Capitalizing on a teachable moment: development of a targeted self-help smoking cessation intervention for patients receiving lung cancer screening. *Lung Cancer*. 2019;130:121-27.
87. van der Aalst CM, de Koning HJ, van den Bergh KA, Willemsen MC, van Klaveren RJ. The effectiveness of a computer-tailored smoking cessation intervention for participants in lung cancer screening: a randomised controlled trial. *Lung Cancer*. 2012;76(2):204-10.
88. Park ER, Gareen IF, Japuntich S, Lennes I, Hyland K, De Mello S, et al. Primary care provider-delivered smoking cessation interventions and smoking cessation among participants in the national lung screening trial. *JAMA Internal Medicine*. 2015;175(9):1509-16.
89. Marshall HM, Courtney DA, Passmore LH, McCaul EM, Yang IA, Bowman RV, et al. Brief tailored smoking cessation counseling in a lung cancer screening population is feasible: a pilot randomized controlled trial. *Nicotine & Tobacco Research*. 2016;18(7):1665-69.
90. Ostroff JS, Copeland A, Borderud SP, Li Y, Shelley DR, Henschke CI. Readiness of lung cancer screening sites to deliver smoking cessation treatment: current practices, organizational priority, and perceived barriers. *Nicotine & Tobacco Research*. 2016;18(5):1067-75.
91. Flynn AE, Peters MJ, Morgan LC. Attitudes towards lung cancer screening in an Australian high-risk population. *Lung Cancer Int*. 2013;2013:789057-57.

92. Manners D, Wilcox H, McWilliams A, Piccolo F, Liira H, Brims F. Current lung cancer screening practice amongst general practitioners in Western Australia: a cross-sectional study. *Internal Medicine Journal*. 2018;48(1):78-80.
93. Mazzone P, Powell CA, Arenberg D, Bach P, Detterbeck F, Gould MK, et al. Components necessary for high-quality lung cancer screening: American college of chest physicians and American thoracic society policy statement. *Chest*. 2015;147(2):295-303.
94. Wiener RS, Gould MK, Arenberg DA, Au DH, Fennig K, Lamb CR, et al. An official American Thoracic Society/American College of Chest Physicians policy statement: implementation of low-dose computed tomography lung cancer screening programs in clinical practice. *American Journal of Respiratory and Critical Care Medicine*. 2015;192(7):881-91.
95. Weinstock T, Kidambi P, Channick CL, Michaud GC, Broaddus C, Makani SS, et al. Implementation of lung cancer screening programs with low-dose computed tomography in clinical practice. *Annals of the American Thoracic Society*. 2016;13(3):425-27.
96. Expert Panel on Thoracic I, Donnelly EF, Kazerooni EA, Lee E, Henry TS, Boiselle PM, et al. ACR Appropriateness Criteria Lung Cancer Screening. *Journal of the American College of Radiology*. 2018;15(11S):S341-S46.
97. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e78S-e92S.
98. American Thoracic Society and American Lung Association. Implementation guide for lung cancer screening New York: American Thoracic Society; 2019. Available from: https://www.lungcancerscreeningguide.org/.
99. (NHS) NHS. Targeted screening for lung cancer with low radiation dose computed tomography: standard protocol prepared for the Targeted Lung Health Checks Programme. England: NHS, 2019.
100. Baldwin D, Callister M, Akram A, Cane P, Draffan J, Franks K, et al. British Thoracic Society quality standards for the investigation and management of pulmonary nodules. *BMJ Open Respiratory Research*. 2018;5(1):e000273.
101. Kauczor HU, Bonomo L, Gaga M, Nackaerts K, Peled N, Prokop M, et al. ESR/ERS white paper on lung cancer screening. *European Respiratory Journal*. 2015;46(1):28-39.
102. McKee BJ, McKee AB, Flacke S, Lamb CR, Hesketh PJ, Wald C. Initial experience with a free, high-volume, low-dose CT lung cancer screening program. *Journal of the American College of Radiology*. 2013;10(8):586-92.
103. Begnaud A, Hall T, Allen T. Lung cancer screening with low-dose CT: implementation amid changing public policy at one health care system. *American Society of Clinical Oncology Educational Book*. 2016;35:e468-75.
104. Okereke IC, Bates MF, Jankowich MD, Rounds SI, Kimble BA, Baptiste JV, et al. Effects of implementation of lung cancer screening at one Veterans Affairs medical center. *Chest*. 2016;150(5):1023-29.
105. Ahmed A, Verma N, Barreto I, Mohammed TL. Low-dose Lung cancer screening at an academic medical center: initial experience and dose reduction strategies. *Academic Radiology*. 2018;25(8):1025-30.
106. Brenner AT, Cubillos L, Birchard K, Doyle-Burr C, Eick J, Henderson L, et al. Improving the implementation of lung cancer screening guidelines at an academic primary care practice. *Journal of Healthcare Quality*. 2018;40(1):27-35.
107. Cattaneo SM, 2nd, Meisenberg BR, Geronimo MCM, Bhandari B, Maxted JW, Brady-Copertino CJ. Lung cancer screening in the community setting. *Ann Thorac Surg*. 2018;105(6):1627-32.
108. Fabbrini AE, Lillie SE, Partin MR, Fu SS, Clothier BA, Bangerter AK, et al. Initial results of a lung cancer screening demonstration project: a local program evaluation. *American Journal of Managed Care*. 2018;24(6):272-77.
109. Lanni TB, Jr., Stevens C, Farah M, Boyer A, Davis J, Welsh R, et al. Early results From the implementation of a lung cancer screening program: the Beaumont Health System experience. *American Journal of Clinical Oncology*. 2018;41(3):218-22.
110. Strong A. A nurse practitioner's experience in the development and implementation of a lung cancer screening program. *Journal of the Advanced Practitioner in Oncology*. 2018;9(5):524-29.
111. Shields LB, Wilkett Barnes JG, Buckley C, Mikos GJ, Rogers KN, Hamm JT, et al. Multidisciplinary approach to low-dose CT screening for lung cancer in a metropolitan community. *Family Practice*. 2019;04:04.
112. Kinsinger LS, Anderson C, Kim J, Larson M, Chan SH, King HA, et al. Implementation of lung cancer screening in the Veterans Health Administration. *JAMA Internal Medicine*. 2017;177(3):399-406.
113. Gould MK, Sakoda LC, Ritzwoller DP, Simoff MJ, Neslund-Dudas CM, Kushi LH, et al. Monitoring lung cancer screening use and outcomes at four cancer research network sites. *Annals of the American Thoracic Society*. 2017;14(12):1827-35.

114. Gesthalter YB, Koppelman E, Bolton R, Slatore CG, Yoon SH, Cain HC, et al. Evaluations of implementation at early-adopting lung cancer screening programs: lessons learned. *Chest*. 2017;152(1):70-80.
115. Crosbie PA, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D, et al. Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester. *Thorax*. 2019;74(4):405-09.
116. Marcus PM, Lenz S, Sammons D, Black W, Garg K. Recruitment methods employed in the National Lung Screening Trial. *J Med Screen*. 2012;19(2):94-102.
117. Qiu R, Copeland A, Sercy E, Porter NR, McDonnell KK, Eberth J. Planning and implementation of Low-Dose Computed Tomography lung cancer screening programs in the United States. *Clinical Journal of Oncology Nursing*. 2016;20(1):52-8.
118. Copeland A, Criswell A, Ciupek A, King JC. Effectiveness of lung cancer screening implementation in the community setting in the United States. *Journal of Oncology Practice/American Society of Clinical Oncology*. 2019;15(7):e607-e15.
119. Lillie SE, Fu SS, Fabbrini AE, Rice KL, Clothier B, Nelson DB, et al. What factors do patients consider most important in making lung cancer screening decisions? Findings from a demonstration project conducted in the Veterans Health Administration. *Lung Cancer*. 2017;104:38-44.
120. Zeliadt SB, Hoffman RM, Birkby G, Eberth JM, Brenner AT, Reuland DS, et al. Challenges implementing lung cancer screening in federally qualified health centers. *American Journal of Preventive Medicine*. 2018;54(4):568-75.
121. Richards TB, Doria-Rose VP, Soman A, Klabunde CN, Caraballo RS, Gray SC, et al. Lung cancer screening inconsistent with U.S. Preventive Services Task Force recommendations. *American Journal of Preventive Medicine*. 2019;56(1):66-73.
122. Modin HE, Fathi JT, Gilbert CR, Wilshire CL, Wilson AK, Aye RW, et al. Pack-year cigarette smoking history for determination of lung cancer screening eligibility. Comparison of the electronic medical record versus a shared decision-making conversation. *Annals of the American Thoracic Society*. 2017;14(8):1320-25.
123. O'Brien MA, Sullivan F, Carson A, Siddiqui R, Syed S, Paszat L. Piloting electronic screening forms in primary care: findings from a mixed methods study to identify patients eligible for low dose CT lung cancer screening. *BMC Family Practice*. 2017;18(1):95.
124. Veronesi G, Colombo P, Novellis P, Crepaldi A, Lutman RF, Dieci E, et al. Pilot study on use of home telephoning to identify and recruit high-risk individuals for lung cancer screening. *Lung Cancer*. 2017;105:39-41.
125. Cole AM, Pflugeisen B, Schwartz MR, Miller SC. Cross sectional study to assess the accuracy of electronic health record data to identify patients in need of lung cancer screening. *BMC Res Notes*. 2018;11(1):14.
126. Lee J, Lim J, Kim Y, Kim HY, Goo JM, Lee CT, et al. Development of protocol for Korean Lung Cancer Screening Project (K-LUCAS) to evaluate effectiveness and feasibility to implement a national cancer screening program. *Cancer Research & Treatment*. 2019;19:19.
127. Pinsky PF. Lung cancer screening with low-dose CT: A world-wide view. *Translational Lung Cancer Research*. 2018;7(3):234-42.
128. Patel S. Attitudes to participation in a lung cancer screening trial: a qualitative study. *Thorax*. 2012.
129. Ali N, Lifford KJ, Carter B, McRonald F, Yadegarfar G, Baldwin DR, et al. Barriers to uptake among high-risk individuals declining participation in lung cancer screening: a mixed methods analysis of the UK Lung Cancer Screening (UKLS) trial. *BMJ Open*. 2015;5(7):e008254.
130. Field JK, Devaraj A, Duffy SW, Baldwin DR. CT screening for lung cancer: is the evidence strong enough? *Lung Cancer*. 2016;91:29-35.
131. Quaife SL, Marlow LAV, McEwen A, Janes SM, Wardle J. Attitudes towards lung cancer screening in socioeconomically deprived and heavy smoking communities: informing screening communication. *Health Expectations*. 2017;20(4):563-73.
132. Quaife SL, Vrinten C, Ruparel M, Janes SM, Beeken RJ, Waller J, et al. Smokers' interest in a lung cancer screening programme: a national survey in England. *BMC Cancer*. 2018;18(1):497.
133. Jonnalagadda S, Bergamo C, Lin JJ, Lurslurchachai L, Diefenbach M, Smith C, et al. Beliefs and attitudes about lung cancer screening among smokers. *Lung Cancer*. 2012;77(3):526-31.
134. Carter-Harris L, Brandzel S, Wernli KJ, Roth JA, Buist DSM. A qualitative study exploring why individuals opt out of lung cancer screening. *Family Practice*. 2017;34(2):239-44.
135. Carter-Harris L, Gould MK. Multilevel barriers to the successful implementation of lung cancer screening: why does it have to be so hard? *Annals of the American Thoracic Society*. 2017;14(8):1261-65.
136. Gressard L, DeGroff AS, Richards TB, Melillo S, Kish-Doto J, Heminger CL, et al. A qualitative analysis of smokers' perceptions about lung cancer screening. *BMC Public Health*. 2017;17(1):589.

137. Tammemagi MC, Schmidt H, Martel S, McWilliams A, Goffin JR, Johnston MR, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. *Lancet Oncology*. 2017;18(11):1523-31.
138. Rzyman W, Dziedzic R, Jelitto-Gorska M, Biadacz I, Ksiazek J, Siebert J, et al. Results of an open-access lung cancer screening program with low-dose computed tomography: the Gdansk experience. *Polskie Archiwum Medycyny Wewnetrznej*. 2015;125(4):232-9.
139. Garrido P, Sanchez M, Belda Sanchis J, Moreno Mata N, Artal A, Gayete A, et al. Reflections on the implementation of Low-Dose Computed Tomography screening in individuals at high risk of lung cancer in Spain. *Archivos de Bronconeumologia*. 2017;53(10):568-73.
140. Field J, Duffy S, Baldwin D, Whynes D, Devaraj A, Brain K, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax*. 2016;71(2):161-70.
141. Ruparel M, Quaife SL, Ghimire B, Dickson JL, Bhowmik A, Navani N, et al. Impact of a lung cancer screening information film on informed decision-making: a randomized trial. *Annals of the American Thoracic Society*. 2019;16(6):744-51.
142. 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*. 2018;124:233-40.
143. dos Santos RS, Franceschini JP, Chate RC, Ghefter MC, Kay F, Trajano AL, et al. Do current lung cancer screening guidelines apply for populations with high prevalence of granulomatous disease? Results from the First Brazilian Lung Cancer Screening Trial (BRELT1). *Ann Thorac Surg*. 2016;101(2):481-6; discussion 87-8.
144. Callister M. Optimal approach to integrate smoking cessation into screening program. *Journal of Thoracic Oncology*. 2018;13 (10 Supplement):S276.
145. Huo J, Shen C, Volk RJ, Shih YT. Use of CT and chest radiography for lung cancer screening before and after publication of screening guidelines: intended and unintended uptake. *JAMA Internal Medicine*. 2017;177(3):439-41.
146. Cardarelli R, Reese D, Roper KL, Cardarelli K, Feltner FJ, Studts JL, et al. Terminate lung cancer (TLC) study: a mixed-methods population approach to increase lung cancer screening awareness and low-dose computed tomography in Eastern Kentucky. *Cancer Epidemiology*. 2017;46:1-8.
147. Begnaud AL, Joseph AM, Lindgren BR. Randomized electronic promotion of lung cancer screening: a pilot. *JCO Clinical Cancer Informatics*. 2017;1:1-6.
148. Black L. Lung cancer screening: implementation of and barriers to a nurse practitioner-led program. *Clinical Journal of Oncology Nursing*. 2018;22(6):601-05.
149. van Iersel CA, de Koning HJ, Draisma G, Mali WPTM, Scholten ET, Nackaerts K, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *International Journal of Cancer*. 2007;120(4):868-74.
150. Lee JW, Kim HY, Goo JM, Kim EY, Lee SJ, Kim TJ, et al. Radiological report of pilot study for the Korean Lung Cancer Screening (K-LUCAS) Project: feasibility of implementing lung imaging reporting and data system. *Korean Journal of Radiology*. 2018;19(4):803-08.
151. Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax*. 2016;71(2):161.
152. Cassidy A, Myles JP, van Tongeren M, Page RD, Liloglou T, Duffy SW, et al. The LLP risk model: an individual risk prediction model for lung cancer. *British Journal of Cancer*. 2008;98(2):270-6.
153. Weber M, Yap S, Goldsbury D, Manners D, Tammemagi M, Marshall H, et al. Identifying high risk individuals for targeted lung cancer screening: independent validation of the PLCOm2012 risk prediction tool. *International Journal of Cancer*. 2017;141(2):242-53.
154. Aberle DR. Implementing lung cancer screening: the US experience. *Clinical Radiology*. 2017;72(5):401-06.
155. Li J, Chung S, Wei EK, Luft HS. New recommendation and coverage of low-dose computed tomography for lung cancer screening: uptake has increased but is still low. *BMC Health Services Research*. 2018;18(1):525.
156. Jessup DL, Glover Iv M, Daye D, Banzi L, Jones P, Choy G, et al. Implementation of digital awareness strategies to engage patients and providers in a lung cancer screening program: retrospective study. *Journal of Medical Internet Research*. 2018;20(2):e52.
157. Springer SM, McFall A, Hager P, Percy-Laury A, Vinson CA. Lung cancer screening: an emerging cancer control issue presents opportunities for an awareness campaign in rural Michigan. *Cancer Causes & Control*. 2018;29(12):1257-63.

158. Lowenstein LM, Deyter GMR, Nishi S, Wang T, Volk RJ. Shared decision-making conversations and smoking cessation interventions: critical components of low-dose CT lung cancer screening programs. *Translational Lung Cancer Research*. 2018;7(3):254-71.
159. Brenner AT, Malo TL, Margolis M, Elston Lafata J, James S, Vu MB, et al. Evaluating shared decision making for lung cancer screening. *JAMA Internal Medicine*. 2018;178(10):1311-16.
160. Lau YK, Caverly TJ, Cao P, Cherng ST, West M, Gaber C, et al. Evaluation of a personalized, Web-based decision aid for lung cancer screening. *American Journal of Preventive Medicine*. 2015;49(6):e125-9.
161. Kinsinger LS, Anderson C, Kim J, Larson M, Chan SH, King HA, et al. Implementation of lung cancer screening in the Veterans Health Administration: supplementary file. . *JAMA Internal Medicine*. 2017;177(3):399-406.
162. American College of Radiology and Society of Thoracic Radiology. ACR–STR practice parameter for the performance and reporting of lung cancer screening thoracic computed tomography. Reston, VA: American College of Radiology, 2019.
163. Silva M, Pastorino U, Sverzellati N. Lung cancer screening with low-dose CT in Europe: strength and weakness of diverse independent screening trials. *Clinical Radiology*. 2017;72(5):389-400.
164. Ferketich AK, Otterson GA, King M, Hall N, Browning KK, Wewers ME. A pilot test of a combined tobacco dependence treatment and lung cancer screening program. *Lung Cancer*. 2012;76(2):211-5.
165. Taylor KL, Hagerman CJ, Luta G, Bellini PG, Stanton C, Abrams DB, et al. Preliminary evaluation of a telephone-based smoking cessation intervention in the lung cancer screening setting: a randomized clinical trial. *Lung Cancer*. 2017;108:242-46.
166. Zeliadt SB, Heffner JL, Sayre G, Klein DE, Simons C, Williams J, et al. Attitudes and perceptions about smoking cessation in the context of lung cancer screening. *JAMA Internal Medicine*. 2015;175(9):1530-7.
167. Ashraf H, Tønnesen P, Pedersen JH, Dirksen A, Thorsen H, Døssing M. Effect of CT screening on smoking habits at 1-year follow-up in the Danish Lung Cancer Screening Trial (DLCST). *Thorax*. 2009;64(5):388-92.
168. Hinde S, Crilly T, Balata H, Bartlett R, Crilly J, Barber P, et al. The cost-effectiveness of the Manchester 'lung health checks', a community-based lung cancer low-dose CT screening pilot. *Lung Cancer*. 2018;126:119-24.
169. Kumar V, Cohen JT, van Klaveren D, Soeteman DI, Wong JB, Neumann PJ, et al. Risk-targeted lung cancer screening: a cost-effectiveness analysis. *Annals of Internal Medicine*. 2018;168(3):161-69.
170. Yang SC, Lai WW, Lin CC, Su WC, Ku LJ, Hwang JS, et al. Cost-effectiveness of implementing computed tomography screening for lung cancer in Taiwan. *Lung Cancer*. 2017;108:183-91.
171. Tomonaga Y, Ten Haaf K, Frauenfelder T, Kohler M, Kouyos RD, Shilaih M, 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.
172. Toumazis I, Tsai EB, Erdogan SA, Han SS, Wan W, Leung A, et al. Cost-effectiveness analysis of lung cancer screening accounting for the effect of indeterminate findings. *JNCI Cancer Spectrum*. 2019;3(3).
173. Wade S, Weber M, Caruana M, Kang YJ, Marshall H, Manser R, et al. Estimating the cost-effectiveness of lung cancer screening with Low-Dose Computed Tomography for high-risk smokers in Australia. *Journal of Thoracic Oncology*. 2018;13(8):1094-105.
174. Gareen IF, Black WC, Tosteson TD, Wang Q, Sicks JD, Tosteson ANA. Medical care costs were similar across the Low-Dose Computed Tomography and Chest X-Ray arms of the National Lung Screening Trial despite different rates of significant incidental findings. *Medical Care*. 2018;56(5):403-09.
175. Chung JM, Simmerman EL, Sadek RF, Wojtowicz S, Dillard TA, Albo D, et al. Financial analysis of free lung cancer screening program shows profitability using broader NCCN guidelines. *Ann Thorac Surg*. 2019;107(3):885-90.
176. Marshall HM, Finn N, Bowman RV, Passmore LH, McCaul EM, Yang IA, et al. The cost of screening for lung cancer in Australia. *Internal Medicine Journal*. 2019;23:23.
177. Rankin N, Weber M, Luo Q, Wade S, Hughes S, Fong K, et al. Lung Cancer Pathways: a five-year program to reduce impact through epidemiological modelling and investment in prioritized interventions. *Journal of Thoracic Oncology*. 2017;12(11 Suppl 2):TBC.
178. Norman R, Moorin R, Maxwell S, Robinson S, Brims F. Public attitudes on lung cancer screening and radiation risk: a discrete choice experiment. *Values in Health*. 2019;Under revision.
179. Murray SR, Murchie P, Campbell N, Walter FM, Mazza D, Habgood E, et al. Protocol for the CHEST Australia Trial: a phase II randomised controlled trial of an intervention to reduce time-to-consult with symptoms of lung cancer. *BMJ Open*. 2015;5(5):e008046.
180. Emery JD, Murray SR, Walter FM, Martin A, Goodall S, Mazza D, et al. The Chest Australia Trial: a randomised controlled trial of an intervention to increase consultation rates in smokers at risk of lung cancer. *Thorax*. 2019;74(4):362-70.

181. Rankin NM, York S, Stone E, Barnes D, McGregor D, Lai M, et al. Pathways to lung cancer diagnosis: a qualitative study of patients and general practitioners about diagnostic and pretreatment intervals. *Annals of the American Thoracic Society*. 2017;14(5):742-53.
182. Jong KE, Vale PJ, Armstrong BK. Rural inequalities in cancer care and outcome. *Medical Journal of Australia*. 2005;182(1):13-4.
183. Emery JD, Walter FM, Gray V, Sinclair C, Howting D, Bulsara M, et al. Diagnosing cancer in the bush: a mixed methods study of GP and specialist diagnostic intervals in rural Western Australia. *Family Practice*. 2013;30(5):541-50.
184. Underhill C, Bartel R, Goldstein D, Snodgrass H, Begbie S, Yates P, et al. Mapping oncology services in regional and rural Australia. *Aust J Rural Health*. 2009;17(6):321-9.
185. Tracey E, McCaughan B, Badgery-Parker T, Young J, Armstrong B. Survival of Australian lung cancer patients and the impact of distance from and attendance at a thoracic specialist centre: a data linkage study. *Thorax*. 2015;70(2):152-60.
186. Zucca A, Boyes A, Newling G, Hall A, Girgis A. Travelling all over the countryside: travel-related burden and financial difficulties reported by cancer patients in New South Wales and Victoria. *Australian Journal of Rural Health*. 2011;19(6):298-305.
187. Platt V, O'Connor K, Coleman R. Improving regional and rural cancer services in Western Australia. *Australian Journal of Rural Health*. 2015;23(1):32-39.
188. Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, et al. European position statement on lung cancer screening. *The Lancet Oncology*. 2017;18(12):e754-e66.
189. National Health Service. NHS to rollout lung cancer scanning trucks across the country London, UK: NHS; 2019 [29 October, 2019]. Available from: https://www.england.nhs.uk/2019/02/lung-trucks/.
190. Heijnsdijk EA, Csanádi M, Gini A, ten Haaf K, Bendes R, Anttila A, et al. All-cause mortality versus cancer-specific mortality as outcome in cancer screening trials: a review and modeling study. *Cancer Medicine*. 2019;8(13):6127-38.
191. Wille MM, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J, et al. Results of the randomized Danish lung cancer screening trial with focus on high-risk profiling. *American Journal of Respiratory and Critical Care Medicine*. 2016;193(5):542-51.
192. Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G, et al. Long-term follow-up results of the DANTE trial, a randomized study of lung cancer screening with spiral computed tomography. *American Journal of Respiratory and Critical Care Medicine*. 2015;191(10):1166-75.
193. Toyoda Y, Nakayama T, Kusunoki Y, Iso H, Suzuki T. Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography. *British Journal of Cancer*. 2008;98(10):1602-07.
194. Hinde S, Crilly T, Balata H, Bartlett R, Crilly J, Barber P, et al. The cost-effectiveness of the Manchester 'lung health checks', a community-based lung cancer low-dose CT screening pilot. *Lung Cancer*. 2018;126:119-24.

Table 3: Lung cancer trials background information, mortality, all-cause mortality and early detection rates(8)

Trial (no randomised) Country	**Country or jurisdiction Year start**	**Screening program**	**Screening eligibility: Population age; smoking history** (Smoking history at randomisation)	**Years since quit**	**Screening interval (total no of rounds)**	**Follow Up years**	**Lung cancer mortality, (CI:95%)**	**All-cause mortality (CI:95%)**	**Early detection (stage I) (CI:95%)**
NLST(59) (53,454)	US, 2002	LDCT vs CXR	55–74; ≥30 pack-years in current smokers and ≥30 pack-years former smokers who quit <15 years ago	≤15	Baseline and 2 annual repeats (3)	7.4	20.0% (95% CI: 6.8–26.7)	6.7% (1.2–13.6)	61.6% detected at stage IA or B
NELSON (37) (15,822)	Netherlands & Belgium, 2003	LDCT vs no screening	50–75; ≥15 cigs/day for ≥25yrs or ≥10 cigs/day for ≥30 years (42 pack-years)	<10	Baseline and at 1, 3 and 5 years (4)	10	26% (95% CI: 0.46–1.19, p=0.21)	NR	69% detected at stage IA or B
DLCST(191) (4104)	Denmark 2004	LDCT vs no screening	50–70; ≥20 pack-years (36 pack-years)	<10	Baseline and 4 annual repeats (5)	10	HR = 1.03 (0.66–1.60)	HR = 1.01 (0.82–1.25)	T1N0M0 = 41%; (Stage I & II = 54%)
ITALUNG(40) (3206)	Italy 2004	LDCT vs no screening	55–69; ≥20 pack-years (43 pack-years)	≤10	Baseline and 3 annual repeats (4)	9	30% (RR=0.70; 0.47 to 1.03)	17% (RR=0.83; 0.67 to 1.03)	36% detected at stage IA or B
DANTE(192) (2450)	Italy 2001	Baseline CXR, sputum cytology & LDCT vs usual care	60–74, ≥20 pack-years (45 pack-years)	<10	Baseline and 4 annual repeats (5)	8.35 median	HR = 0.993; 0.688–1.433	HR = 0.947; 0.769–1.165	47 of 66 (70%) of CT detected LC detected as stage I
MILD(42) (4099)	Italy 2005	LDCT vs no screening	49–75; ≥20 pack-years (43 pack-years)	<10	Baseline and annual or biennial repeats (5 or 3)	10	HR = 1.10, 0.59–2.05	HR = 0.80; 0.57–1.12	53.4% (annual) 45% (biannual) detected at stage I

Trial (no randomised) Country	**Country or jurisdiction Year start**	**Screening program**	**Screening eligibility: Population age; smoking history** (Smoking history at randomisation)	**Years since quit**	**Screening interval (total no of rounds)**	**Follow Up years**	**Lung cancer mortality, (CI:95%)**	**All-cause mortality (CI:95%)**	**Early detection (stage I) (CI:95%)**
UKLS (4055)	UK 2011	LDCT vs no screening	50–75; Liverpool Lung Project (LLP) eligibility criteria for an individual including (>20 pack-years)	NR	Single scan	NR (planned 10yrs)	NR^	NR^	42 screen-detected cancers, 85.7% stage I or II
LUSI(38) (4052)	Germany 2007	LDCT vs no screening	50–69; ≥15 cigs/day for ≥25yrs or ≥10 cigs/day for ≥30 years (36 pack-years)	<10	Baseline and 4 annual repeats (5)	8.8	HR = 0.74; 0.46–1.19	HR = 0.99; 0.79–1.25	NR
Yang(11) (6657)	China 2013	LDCT vs no screening	45–70; ≥20 pack-years (smoking an optional risk factor)	≤15	Baseline and biennial (3)	2	NR	NR	Early stage LC was found in 94.1% (screen) vs 20% (control); 74.1% increase in LDCT detected early stage LC

^Not sufficiently powered (pooled with other trials).

Table 7a: Original evaluation studies reporting outcomes of LDCT screening program implementation

Author, publication year	Brief description (region or institution)	Reported aim, goals or objectives	Population screened; definition of high risk	Recruitment method	Program components reported	Resources developed and/or evaluated	Process or health outcomes	Cost to deliver screening program	Description of smoking cessation component and quit rates
Ahmed et al. 2018(105)	**Single-site evaluation** of LDCT program. (Florida, US)	To assess the lung cancer detection rate, the spectrum of imaging findings and patient radiation dose indices of patients who underwent LDCT	N=272 participants screened	Referrals from clinicians	LDCT protocol and result reporting (Lung-RADS)	Not reported	Process outcomes: Not reported. Health outcomes: Six lung cancers detected (2.2%). Mean number of nodules per examination 0.83	Not reported	Not reported
Begnaud et al. 2016(103)	**Evaluation (descriptive) of single institution** experience of LDCT program (University of Minnesota Health, US)	Experiences implementing an LDCT program including program planning, early implementation and overcoming barriers	N=572 participants screened. Centers for Medicare & Medicaid Services (CMS) final coverage determination used for eligibility	Referred by credentialled provider	Eligibility; recruitment; education; smoking cessation resources; shared-decision making and counselling; result reporting (Lung-RADS)	Paper given to eligible LDCT patients, *Lung Cancer Screening, Frequently Asked Questions and Resources to Help You Quit Smoking*; Set up a call centre, have certified nurse specialists and a physician	Process outcomes: Poorly described but shared decision-making improved after the CMS mandate from rates of about 13% to about 46%–50% of consultations Health outcomes: Not reported beyond Lung-RADS status; no definitive	Not reported but single scan cost was initially $150 per person; after CMS decision, insurance coverage made CT scan free for Medicare recipients	Provided patients eligible for screening with smoking cessation resources/information. No quit rate data reported

Author, publication year	Brief description (region or institution)	Reported aim, goals or objectives	Population screened; definition of high risk	Recruitment method	Program components reported	Resources developed and/or evaluated	Process or health outcomes	Cost to deliver screening program	Description of smoking cessation component and quit rates
							numbers of patients reported		
Black et al. 2018(148)	Implementation of **nurse practitioner program** at a single institution (University of Maryland Medical Centre, US)	Descriptive account of program development, practitioner role and first-year results	96 patients screened in first year; 1 diagnosed with lung cancer	Marketing materials: advertising, social media, website; Presentations to staff via grand rounds and clinical meetings	Program development	Creation of an automated report for the LDCT order in the EHR	Process outcomes: Not reported. Health outcomes: Six lung cancers detected	Not reported	Nurse initiates discussion about cessation (identification of smoking habits, development of a patient-centred plan for cessation, prescription of pharmacologic cessation aids). No quit rate data reported
Brenner et al. 2018(106)	**Pilot study** of LDCT program using Quality Improvement methodology; single institute study. (Large academic primary care practice in North Carolina, US)	Develop and pilot test LDCT program. Three gap areas identified: 1. protocol to complete smoking history collection; 2. visit-based reminder; 3. shared decision-making (SDM) documentation	Catchment of n=13,000 patients; conducted a chart review of n=50 patients; n=644 visit-based reminders	Not reported	Eligibility; recruitment	Staff protocols for collecting smoking histories, offering screening to eligible patients, shared-decision making. Visit-based reminder in EHR for LDCT eligibility, shared-decision	Process outcomes: Collection of smoking histories increased from 2% to 77%. Visit-based reminder reduced cognitive load for physicians. Improved documentation. SDM increased from 0% in 2014	Not reported	Not reported

Author, publication year	Brief description (region or institution)	Reported aim, goals or objectives	Population screened; definition of high risk	Recruitment method	Program components reported	Resources developed and/or evaluated	Process or health outcomes	Cost to deliver screening program	Description of smoking cessation component and quit rates
		and billing procedures				making notes and test ordering	(n=2) to 71%–76% in 2016 (n=33) Health outcomes: Not reported		
Cattaneo et al. 2018(107)	**Single site retrospective audit** of LDCT program implementation (acute care community hospital, Annapolis Maryland, US)	Assessed patient demographics, results, protocol adherence and complications in the first 5 years of an LDCT program	N=1241 participants screened in 5 years. NLST eligibility criteria	Via primary care provider (PCP); PCP education; community education & marketing; LDCT discount offered	Recruitment; screening process; LDCT protocol and result reporting (Lung-RADS)	Not reported	Process outcomes: Less adherence to follow-up compared with NLST Health outcomes: Cancer detection rate 2%, of which 72% stage I. 1.1% invasive biopsies for benign results	Not reported	All participants referred to smoking cessation program. Impact of LDCT on smoking cessation not included in study
Copeland et al. 2019(118)	**Survey** of LDCT centres (165 Screening Centres of Excellence across 34 states, US)	Assess screening implementation during first year of implementation in US	Not reported	Counselling and shared-decision making led by a qualified practitioner precedes LDCT screening	Recruitment; smoking cessation resources; result reporting (Lung-RADS)	Not reported	Process outcomes: >50% experienced insurance and billing issues; lack of participant awareness; workflow issues and referral barriers Health outcomes: Stage I	Not reported	Smoking cessation services offered to current smokers seeking screening. Three common approaches: Quitline, counselling service and printed material. No quit rates reported

Author, publication year	Brief description (region or institution)	Reported aim, goals or objectives	Population screened; definition of high risk	Recruitment method	Program components reported	Resources developed and/or evaluated	Process or health outcomes	Cost to deliver screening program	Description of smoking cessation component and quit rates
							NSCLC most common diagnosis (49%)		
Fabbrini et al. 2018(108)	**Initial results** of lung cancer screening program	Feasibility testing LDCT	N=178 patients screened; NLST eligibility criteria	Identified via EHR and mailed SDM materials and invitation letter	Recruitment; eligibility; smoking cessation; education; SDM; result reporting	Not reported	Process outcomes: 178/918 patients invited for LDCT completed a. LDCT Health outcomes: 2/178 patients had malignant nodules	Not reported	All patients had access to a smoking cessation program. No quit rates reported
Gesthalter et al. 2017(114)	**Qualitative evaluation** of LDCT program (Three VA medical centres in three states, US)	Evaluate experience of early adopting LDCT programs and identify facilitators and barriers	Not reported	EHR prompt for PCP to discuss eligibility at 2 sites	Screening protocols; eligibility; coordinator role; SDM; Multidisciplinary team (MDT); screening registry; tobacco treatment	Not reported	Process outcomes: Not reported Health outcomes: Not reported	Not reported	1/3 sites integrated strategies for cessation: Coordinator training, automatic referrals, immediate psychologist consult and written materials at multiple time points. No quit rates reported

Author, publication year	Brief description (region or institution)	Reported aim, goals or objectives	Population screened; definition of high risk	Recruitment method	Program components reported	Resources developed and/or evaluated	Process or health outcomes	Cost to deliver screening program	Description of smoking cessation component and quit rates
Kinsinger et al. 2017(112)	**Evaluation of 8 centres** in the Veterans Health Administration (VHA, US)	Describe experiences implementing LDCT program and estimate eligibility rates	2106 patients screened of 4246 eligible	Eligibility algorithm applied to EHR with PCP to establish eligibility	Eligibility; recruitment; education; coordinator role	Implementation guide, including resources, tools and evaluation plan, with patient education materials and nodule guidelines	Process outcomes: 57.7% uptake of LDCT. Days from initial scan to cancer diagnosis was 137 days Health outcomes: 3.5% of patients screened underwent further tests. 1.5% diagnosed with LC	Not reported	Smoking cessation program acknowledged as component. Quit rates not reported. Acknowledged that more needs to be understood about the smoking cessation experience of those who were screened
Lanni et al. 2018(109)	**Single institution evaluation** of 1 year screening program (Beaumont Health System, MI, US)	Compare outcomes and costs associated with developing and implementing LDCT program	N=1065 patients screened; Eligibility based on NCCN guidelines	Physician order, written or electronic	Result reporting (Lung-RADS); working group LCS program development	A low-dose protocol was developed using the ACR Lung Cancer Screening Center Technical Specifications; IT resources developed to ensure documentation; location of CT scanners reviewed	Process outcomes: Not reported Health outcomes: 21.7% of patients screened underwent further tests. 1.6% patients diagnosed with lung cancer	Not able to calculate additional cost, but additional net revenue for LDCT program was $1763 per patient, which helped cover screening, smoking cessation education, clinical staff and registry	Smoking cessation education. Quit rates not reported

Author, publication year	Brief description (region or institution)	Reported aim, goals or objectives	Population screened; definition of high risk	Recruitment method	Program components reported	Resources developed and/or evaluated	Process or health outcomes	Cost to deliver screening program	Description of smoking cessation component and quit rates
McKee et al. 2013(102)	**Description** of free CT-screening program in the US (Lahey Hospital & Medical Center, MA, US)	Report the critical elements and initial results of an LDCT program	N=500 screened. NLST eligibility criteria	PCP referral; toll-free referral line	Patient access (cost to patients); business considerations (scanner access, capacity staffing, financial impact); infrastructure; standardised reporting; physician and patient education	Radiology dept working group developed LDCT program elements: toll-free number; intake forms; call centre script; FAQ; patient information and management database; patient letter library; education program; LDCT scanning protocols	Process outcomes: Not reported Health outcomes: 3 of 500 patients were diagnosed with early stage lung cancer	Not reported but acknowledges importance of reimbursement for equitable access	Smoking cessation education material. Quit rates not reported
Okereke et al. 2016(104)	**Single institution evaluation** of 1-year screening program (community teaching	Evaluate the results of an LDCT program	N=1832 patients screened. NLST eligibility criteria	EHR prompt for PCP	Eligibility; recruitment; coordinator role; LDCT scanning protocols	Clinical reminder in electronic health record (EHR) to prompt physicians of eligible patients. Nurse	Process outcomes: Not reported Health outcomes: 55/1932 (2.8%) were diagnosed with LC. LC detection increased from	Not reported	Not reported

Author, publication year	Brief description (region or institution)	Reported aim, goals or objectives	Population screened; definition of high risk	Recruitment method	Program components reported	Resources developed and/or evaluated	Process or health outcomes	Cost to deliver screening program	Description of smoking cessation component and quit rates
	hospital, Rhode Is, US)					coordinator facilitated scan scheduling and patient reminders	2.4 to 6.7 cases per month. Early stage detection increased from 37% to 60%		
Qiu, et al. 2016(117)	**Mixed-methods study** involving Screening Centers of Excellence (n=64 centres, US)	Identify characteristics and barriers to the development and implementation of LDCT programs	70% reported use of NCCN or NLST eligibility criteria	Not reported	Implementation; screening guidelines; eligibility criteria; MDTs; education	Not reported	Process outcomes: Not reported Health outcomes: Not reported	Average reported cost for LDCT across n=18 centres was $100–$199. No whole program costs reported	Not reported
Shields et al. 2019(111)	**Observational cohort** study to evaluate LDCT screening program in single institution (metro community Kentucky, US)	Evaluate the impact of two years of LDCT program; specifically LDCT screening, smoking prevention/ cessation and diagnosis of lung cancer	N=4170 patients underwent screening. 55–80yrs, current or former smoker, <15 yrs since quit, with >30 PYH	Eligibility algorithm applied to EHR to prompt PCP	Recruitment; shared decision-making; LDCT scanning protocols; smoking cessation; education; follow-up; treatment planning; MDT; coordinator role	Not reported	Process outcomes: Not reported Health outcomes: 70/4170 (1.2%) patients screened were diagnosed with LC; most common stage I (54.3%)	Not reported	All participants were offered individual cessation counselling (1:1) or group sessions. Final participant numbers are not stated. However, 1:1 counselling had lower quit rates than group sessions (28% vs 42%). 2653 (63.6%) participants continued to

Author, publication year	Brief description (region or institution)	Reported aim, goals or objectives	Population screened; definition of high risk	Recruitment method	Program components reported	Resources developed and/or evaluated	Process or health outcomes	Cost to deliver screening program	Description of smoking cessation component and quit rates
									smoke (numbers diagnosed with lung cancer are not stated)
Crosbie et al. 2019(115)	UK Lung Health Check (LHC) (community based lung screen service, Manchester, England)	Describe design and evaluate pilot LDCT program (T0)	N=1384/ 1429 (97%) of eligible participants screened. high risk (6-year risk ≥1.51%, PLCOM2012 calculator)	Invite letter to ever-smokers, 55–74yrs, registered general practitioner practices (n=14) to LHC	Recruitment; guidelines for eligibility and nodule management	Not reported	Process outcomes: 26.3% of invited participants attended LHC; High demand – all appointments booked within days Health outcomes N=42/1384 (3%) diagnosed with LC; 80% early stage. False positive rate 44.5%	Not reported	Smoking cessation advice as component of LHC. No quit rate data reported

Author, publication year	Brief description (region or institution)	Reported aim, goals or objectives	Population screened; definition of high risk	Recruitment method	Program components reported	Resources developed and/or evaluated	Process or health outcomes	Cost to deliver screening program	Description of smoking cessation component and quit rates
Crosbie et al. 2019(75)	UK Lung Health Check (LHC) (community based lung screen service, Manchester, England)	Evaluate second round of LDCT program (T1, 12 mths post T0, above)	N=1194/ 1323 eligible participants screened (90%). High-risk eligibility as per T0	Follow-up of T0 participants	As reported above	Not reported	Process outcomes: Not reported Health outcomes: Majority of T1 scans 'negative'. N=19 diagnosed with LC (1.6%); 79% stage 1. False positive rate 3.5%	Not reported	As above
Lee et al. 2018(150)	**Evaluation** of Lung Cancer Screening pilot study (Korea)	Report results from the Korean Lung Cancer Screening pilot study	N=256 screened	Recruited from health check-up centres on smoking cessation clinics	Eligibility; recruitment; LDCT protocols and result reporting; radiation dose	Not reported	Process outcomes: Not reported Health outcomes N=1 diagnosed LC (stage 1A SCLC)	Not reported	Not reported

Table 7b: Studies evaluating specific components of LDCT screening program implementation

Author, pub year	Study description (region or institution)	Component(s) evaluated	Aim, goals or objectives	Participants	Recruitment method	Resources developed and/or evaluated	Outcomes	Barriers/ enablers
Begnaud et al. 2017(147)	**Pilot study** of LDCT promotion program. (University of Minnesota Heath)	Recruitment; eligibility	Whether electronic messaging via patient portal can be used to promote LDCT to possibly eligible persons	Former smokers who visited primary care or pulmonary clinics at the institution within the past 2 years	Randomly selected n=200 that met inclusion criteria from institution to receive promotional materials. Questionnaire to determine LDCT eligibility and smoking history disseminated via patient portal	Electronic messages in patient portal; smoking history questionnaire linked to smoking history in EHR; information about LDCT eligibility, risks and benefits; image scheduling information	Proportion of patients who underwent LDCT following a promotion program: Of n=200 who received promotion, five had LDCT. No statistically significant increase in screening following the promotion program	Inadequate smoking history to determine eligibility for 36% of patients
Brenner 2019 (159)	A **qualitative content analysis** of consultations between 14 patients and their physicians	SDM	To assess the quality of SDM about the initiation of LCS in clinical practice	14 patients eligible for LDCT screening and their respiratory physician	Existing database of recorded consultations	No specific SDM was evaluated but the consultation was coded for use of any tool or discussion	The validated 'Observing Patient Involvement in Decision Making' scale, a 12-item measure of SDM (total score, 0-100 points, where 0 indicates no evidence and 100 indicates evidence at highest skill level); time spent discussing LCS during visits; and evidence of decision aid use	Not reported

Author, pub year	Study description (region or institution)	Component(s) evaluated	Aim, goals or objectives	Participants	Recruitment method	Resources developed and/or evaluated	Outcomes	Barriers/ enablers
Cardarelli et al. 2017(146)	**Campaign effectiveness** of Terminate Lung Cancer (TLC) program. (Two targeted Eastern Kentucky regions)	Recruitment	Motivate patients to approach their health providers about their options for LDCT	High-risk: 55–77 years of age, 30 pack-years of smoking, current or former smokers (quit <15 years)	Individuals recruited for focus groups to inform campaign. Recruited from local communities using client files	Postcard mailings and newspaper ads featuring TLC website address; local public radio coverage; physician information about LDCT guidelines & recommendations	No significant difference in overall exposure across intervention/control regions; significant uptake (exceeding the upper control limit) of LDCTs in the two intervention regions; 73/145 surveyed individuals indicated exposure to campaign (N=13 quit smoking, N=23 talked to a doctor about quitting, N=7 developed a quit plan, N=4 looked for quitting information and N=41 thought about quitting)	Multiple grant funding was used to fund project. Acknowledged that TV ads weren't used due to costs
Cole et al. 2018(125)	**Cross-sectional study** to assess accuracy of EHR data to identify potential patients for LDCT (community-based healthcare system in the Pacific Northwest, US)	Eligibility	Assess sensitivity, specificity, and +ve/-ve predictive value of an EHR query compared with patient self-report	N=24 survey participants; 30+ pack-year smoking history (PYH), current smokers or quit <15yrs prior	N=200 randomly sampled for invitation using EHR extracted data; mailed study info sheet, informed consent form & questionnaire	Not reported	Inadequate EHR information to determine the need for LDCT for almost one-third of the participants. Missing data a significant problem	Patients were offered a $5 Starbucks gift card for completing the survey and consent document

Author, pub year	Study description (region or institution)	Component(s) evaluated	Aim, goals or objectives	Participants	Recruitment method	Resources developed and/or evaluated	Outcomes	Barriers/ enablers
Gould et al. 2017(113)	**LDCT screening program characteristics** and data collection approaches (four integrated healthcare systems of the Cancer Research Network)	Eligibility; recruitment; education; result reporting (Lung-RADS)	Describe and share data collection approaches for LDCT; standardise data collection standards	Not reported	LDCT by provider suggestion or patient request. No site employed population-based outreach method. One site used EHR flag, standardised order set to confirm eligibility; one site used electronic consult mechanism to process referrals	Automated data collection to fulfil registry reporting for eligibility, screening occurrence, results, follow-up and lung cancer detection; coordinator education tools for SDM; standardised results template	Most data elements collected from structured fields in EHR; also used standardised order templates, local procedure codes, identifiable hashtags in radiology reports, and natural language processing algorithms	Incomplete smoking history barrier to establishing eligibility. Check-boxes and drop-down menus in EHR converted to free text to minimise inappropriate referrals

Author, pub year	Study description (region or institution)	Component(s) evaluated	Aim, goals or objectives	Participants	Recruitment method	Resources developed and/or evaluated	Outcomes	Barriers/ enablers
Jessup et al. 2018(156)	**Retrospective study** to evaluate campaign effectiveness and education (single institution, CA, US)	Recruitment	To assess the effectiveness of patient and provider-focused LDCT digital awareness campaigns on use of LDCT and visits to institutional online educational content	Campaign targeted current and former smokers aged >55 years; employees and caregivers aged 18 years and older	N/A	Patient campaign: Facebook and Google. Provider campaign: LinkedIn and Twitter. Both patient and provider campaign content linked to appropriate institutional web pages	Click-through-rates above industry averages for consumers and providers. An increase in visits to institutional web pages on LDCT and scheduled LDCTs	Not reported
Li et al. 2018(144)	**A retrospective analysis** of EMR data to assess referrals for LDCT and identify facilitators and barriers to adoption of USPSTF recommendations (large community healthcare system in northern California, US)	Eligibility; guideline implementation	Aimed to assess smoking history, eligibility and medical order documentation and explore patient–provider factors, following guidelines and reimbursement changes	N=999 of n=12,801 eligible patients screened. Eligibility criteria; aged 55–80, smoked more than 30 PYH, current smoker or quit <15 years	Retrospective EMR review	US Preventive Services Task Force eligibility guidelines (and LDCT became a Medicare-covered service)	Substantial variation across providers in referral for LDCT screening; orders increased, but overall remained very low; documentation of smoking history improved substantially from 2010 to 2016 (from 59.2%–77.8%); of the eligible patients, LDCT screening orders increased from 0%–7.3%	Poor smoking history documentation is a barrier to identifying eligible patients

Author, pub year	Study description (region or institution)	Component(s) evaluated	Aim, goals or objectives	Participants	Recruitment method	Resources developed and/or evaluated	Outcomes	Barriers/ enablers
Lillie et al. 2017(119)	**Observational study** to determine factors important to patients with SDM. (Minneapolis VA Lung Cancer Screening Clinical Demonstration Project)	Decision-making	Identify factors important to patients and the effect patient characteristics and benefits and harms have on LDCT screening completion	LDCT-eligible veterans randomised to either direct invitation (mailed with decision aid, N=926) or usual care (provider referral, N=462). N=87 (43.8%) of invited cohort completed 3mth survey	Applied eligibility algorithm to EHR to flag nurse during clinic visit to obtain smoking data. Then allocation 2:1 direct invitation to usual care	A VHA-developed *Screening for Lung Cancer* brochure and invitation letter	Most important decision-making factor was the fear of getting lung cancer (43.5%) and the least was health risks of the LDCT scan (11.6%). 22.7% of eligible patients surveyed completed LDCT	Not reported
Marcus et al. 2012(116)	**Original article** reporting on the methods used to recruit participants to the NLST (NLST centres, US)	Recruitment	Report NLST recruitment methods and associated costs of some methods	n=22 NLST centres; survey completed by centre coordinator and/or another staff member involved in recruitment	Each centre was free to choose its recruitment methods (categorised into direct mail, community outreach and mass media)	Not reported	Enrolment rate and cost per enrolee varied across centres. All centres used direct mail methods at median cost of $101 per enrolee, with approx. n=19,000 participants enrolled. Cost per enrollee for community outreach methods ranged from no cost to $103 (median $4), with n=1000 enrolled. Cost per enrollee for mass media methods ranged	Targeted recruitment of minority populations may be more expensive and time-consuming than recruitment from the general population

Author, pub year	Study description (region or institution)	Component(s) evaluated	Aim, goals or objectives	Participants	Recruitment method	Resources developed and/or evaluated	Outcomes	Barriers/ enablers
							from no cost to $1953 (median $79), with n=4200 enrolled	
Modin et al. 2017(122)	**Retrospective analysis** of EHR vs SDM conversation for eligibility determination (Five hospital LDCT program, Seattle, Washington)	Eligibility; shared decision-making	Compare EMR-extracted data to information derived from SDM for determination of eligibility	All individuals referred or self-referred to LDCT screening program	Referred individuals (primary-carer, specialist, self-referral) contacted by phone by nurse to determine eligibility and conduct SDM	Not reported	EMR incorrectly reported smoking pack-year history 96% of the time compared with SDM; more than 50% of eligible patients would have been overlooked if relying on EHR data alone	Smoking cessation counselling and treatment in conjunction with LDCT screening by tobacco treatment specialist (nurse practitioner)
Ruparel et al, 2019(141)	**Randomised controlled trial** nested within the LSUT study: Information booklet only (control) vs information film plus the same information booklet. (Lung Screen Uptake Trial hospital, London, England)	Decision-making	Aims to evaluate the impact of a novel information film on informed decision-making for individuals considering participating in LDCT screening	N=229 smokers/ former smokers (quit <15yrs ago), aged 60–75 yrs, >30 PYH, >1.51% 6-year LC risk as per $PLCO_{m2012}$ model; and >2.5% 5-year LC risk as per LLPv2 model	Identified from primary care records, invited to a lung health check (LHC) at a local London hospital using one of two sets of randomly allocated invitation materials	Booklet (10p) and film (5.5min) on benefits and harms of LDCT procedure and possible results, created from qualitative data from screening-eligible participants and HCPs	Both groups significantly improved their knowledge scores; both were well received; however, the film had a more significant impact than the booklet alone; but a significant proportion found the film was not helpful for decision-making, perhaps due to perceived bias in favour of LDCT screening	Not reported

Author, pub year	Study description (region or institution)	Component(s) evaluated	Aim, goals or objectives	Participants	Recruitment method	Resources developed and/or evaluated	Outcomes	Barriers/ enablers
Springer et al. 2018(157)	**Description** of campaign implementation (rural Michigan, US)	Multimedia campaign (3-mth campaign, 2015)	Increase awareness of LDCT screening within state's high-risk areas through the use of a variety of media, plus use and marketing of a website providing information and resources	Target audience for campaign were whites, aged 55–80 years	Not reported	Advertising (gas station, convenience store, radio public service announcement) Google Display and AdWords, with digital ads linking users to cancer-control website. Materials compiled into a communication toolkit	Total market impressions for: 1) gas station ads total test of market impressions = 2,577,300; 2) Google Display ads had a click-through rate (CTR) of 0.40% (benchmark 0.15%); 3) Google Search campaign had a CTR of 0.58% (benchmark 1%). The keywords related to smoking had a lower CTR, whereas keywords related to lung cancer had a CTR of 1.5%.	Screening rate could not be reported. Costs not presented but noted that campaign continues when funds are available to do so
Strong 2018[110]	**Original article** outlining nurse perspective of development and implementation of LDCT screening program (regional cancer centre, Virginia, US)	Eligibility; recruitment; LDCT scanning protocol; nurse practitioner	Not reported explicitly but to provide an overview of the nurse practitioner role and the impact on the LDCT screening program	NLST eligibility criteria	N/A	Nurse practitioner performs SDM visit, smoking cessation counselling and education, organises scans, results and follow-up. Recruitment advertised through clinic brochures, TV,	<u>Process outcomes:</u> 'Improved access to care' but this is not quantified <u>Health outcomes:</u> Not reported	Barriers: time (doctor), billing and coding to ensure reimbursement, multiple guidelines with variations, anxiety/stigma in patients, inaccurate smoking histories

Author, pub year	Study description (region or institution)	Component(s) evaluated	Aim, goals or objectives	Participants	Recruitment method	Resources developed and/or evaluated	Outcomes	Barriers/ enablers
						newspaper and magazine advertising		
O'Brien 2017[125]	Comparative study of electronic vs paper form for LDCT eligibility pre-screening	Patient form (electronic vs paper) for eligibility screening	Compare the acceptability and feasibility of using brief electronic vs paper screening forms in primary care to identify eligible patients at high risk of developing lung cancer	Practice-based study, with participants originally identified using the College of Physicians and Surgeons of Ontario database. Patients at each practice also participated	The research team identified and contacted 30 physicians from the database. Patients were recruited if eligible according to age (55-74 years) and had a scheduled appointment with a clinician in one of the six practices	Eligibility pre-screening form to be completed by patients via a link or on a tablet prior to their appointment, or on paper	Process outcomes: Low administrative burden using electronic forms but addition link to appointment system required Health outcomes: Not reported	Facilitators: screening forms easy to complete and served as a reminder for physicians to discuss smoking cessation. Barriers: difficulties with electronic health record and identifying participants

Table 10: RCTs and other studies evaluating smoking cessation interventions

Study (year of publication), Country	Study type	Goals, aims, objectives	Population	Smoking cessation intervention	Comparator (if any)	Outcome measure(s)	Outcomes data associated with smoking cessation or quite rates
Ashraf (2009)(167), Denmark	RCT	The effect on smoking habits of screening with low-dose CT	DLCST participants. Healthy current and former smokers (>4 weeks since smoking cessation) with a tobacco consumption of >20 pack-years	Intervention (LDCT screening) group and control group participants receive minimal smoking cessation counselling (<5 min)	Nil	Smoking status (quit rates and relapse rates) at 1-year follow-up, verified using exhaled carbon monoxide levels	Quit rates similar in study groups at 1-year follow-up, with a net quit rate of 6.0%. Quit rates were higher and relapse rate lower among subjects with initial CT findings that necessitated a repeat scan 3 months later
Brain (2017)(67), UK (n=1546)	Pilot randomised trial	The effect of the baseline scan result on smoking cessation	Participants in UKLS trial, high-risk smokers, 50–75 years	LDCT screening, plus standard smoking cessation information (advice leaflets and list of local National Health Service Stop Smoking services)	No screening, plus standard smoking cessation information (advice leaflets and list of local National Health Service Stop Smoking services)	Self-report at T1 and T2	Net cessation rate 11% in short term and 22% at 2-year follow-up. Quit rates for LDCT screening (24%) vs control (21%) at 2 yrs. Participants who needed additional clinical investigation were more likely to quit (30%) than those with negative results (15%)
Ferketich (2012)(164), US (n=18)	Pilot feasibility	Examine the feasibility of delivering a program that included both tobacco dependence	Volunteers who responded to advertisements placed on our institution's	Point prevalence abstinence and number of quit attempts assessed for 4 months and	Intervention before CT (BCT): Baseline assessment,	Intervention after CT (ACT). Baseline assessment; CT scan; visit to	At 4mths quit rates were 33.3% in the BCT arm and 22.2% in the ACT arm (27.8% overall). At 6mths confirmed abstinence decreased to

		treatment and lung cancer screening	listserves and in medical clinics, ≥50 years, self-reported current smokers with a 20 pack-year history	6 months after the start of the tobacco dependence treatment protocol	medical oncologist visit with quit smoking advice and pharmaco-therapy prescription; 12-week tobacco dependence treatment protocol; CT scan; scan results during medical oncologist visit	medical oncologist with quit smoking advice, scan results and pharmaco-therapy prescription; 12-week tobacco dependence treatment protocol (varenicline or NRT, and weekly telephone counselling)	22.1% in the BCT arm and 11.1% in the ACT arm (16.7% overall), suggesting favour for BCT
Marshall (2016)(89), Australia (n=55)	Pilot RCT		Participants from the QLCSS (age 60–74 years; ≥30 pack-year smoking). Smokers n=55; int grp n=28; control grp n=27. Cigarette consumption 25/day (median); Smoking duration 46 years (median). Fagerström (nicotine) dependence score 6 (median)	Single session of tailored face-to-face counselling on the day of screening CT scan, coupled with audio quit materials, printed quit materials and Quitline contact details	Printed quit materials and Quitline contact details only	Self-reported point prevalence quit rates at 1 year	Intervention had no discernible impact. Quit rate at 1 year: (n=4, 14.3%) in the intervention group and (n=5, 18.5%) in the control group. Combined annual point prevalence quit rate was 16.4%.

Taylor (2017)(165), US (N=92)	Pilot RCT		50–74 years; 20+ pack-year history; current smoker registered for screening	Usual care plus telephone counselling (6 weekly counsellor-initiated calls of 15–20 mins	Usual care (brochure, web reference, contact for local cessation resources, text and App links)	Smoking history, CPD, non-cigarette tobacco use, nicotine dependence and readiness to quit	No significant group difference on self-reported abstinence (UC: 19.6%, N=9 vs. TC: 21.7%, N=10), but significant group difference on biochemically verified abstinence (UC: 4.3%, N=2 vs.TC: 17.4%, N=8)
Joseph (2018)(9), SCALE collaboration of projects	Eight clinical trials, seven funded by the National Cancer Institute and one by the Veterans Health Administration insert more details here 8 trials	The collaboration goal was to support projects testing smoking interventions for patients undergoing LDCT screening and to build an evidence base for effective interventions delivered in this setting. Specific trial aims are described in the article.	Eligible population based on smoking status and age, with specific trial populations defined including Screen eligible versus screen completed participants, people interest in quitting smoking and inclusion of recent quitters.	Various interventions of different intensities, e.g. quit lines, cessation medications and medication sampling, integrated care, training toolkits, digital resources such as web-based programs and text messaging, gain vs. loss message framing	Specified for each of the 8 trials within the publication	A variety of short- and long-term outcomes are monitored across the 8 trials including but not limited to: cessation, abstinence from smoking and quit attempts.	Not reported
Van der Aalst (2012)(87), Netherlands	RCT	Investigate whether a tailored self-help smoking intervention was more effective than a standard	NELSON study participants. Males only, 50 and 75 years, >15 cigarettes a day for >25 years or	Computer based self-help intervention with questionnaire and tailored advice	Standard brochure	Questionnaire to measure smoking behaviour two years after randomisation	No advantage of tailored smoking cessation information over standard self-help information.

		brochure in helping participants to quit	>10 cigarettes a day for >30 years				Overall quit rate for LDCT screening participants was 14%

NRT: nicotine replacement therapy

Table 11a: A summary of cost-effectiveness studies

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
MICROSIMULATION STUDIES									
Toumazis et al. 2019 (172)	Assess the cost-effectiveness of LDCT screening after incorporating the Lung-RADS guidelines to manage indeterminate findings for the US population	General US population born in 1950, single payer/insurer perspective	Annual and biennial screening. Varied starting and stopping ages between 50–65, and 70–80, in 5-year increments. Varied smoking exposure: 20, 30, 40 pack-years and 10, 15 and 20 years since cessation	Risk of developing lung cancer based on Meza et al (2008) data. Natural history model applied to cases once they occurred calibrated to NLST and PLCO. Applied Lung RADS screening guidelines and counterfactuals to the microsimulation .	QALYs—health utilities from the literature. Included short-term disutility (loss of QoL) due to indeterminate findings. Cases that did not have further cancer sequelae returned to normal QoL	LDCT screen, SDM, diagnostic CT, invasive procedure and PET. Treatment interventions at initial, continuing and terminal stages for each: surgery, chemo, RT, supportive care, palliative care	Cost–utility analysis (cost per QALY)	Microsimulation CISNET model	Life history (of one million men and women, separately); 3%

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
Treskova et al. 2017(71)	Investigate the effects of eligibility criteria and nodule management on the benefits, harms and cost-effectiveness of LS with LDCT in a population-based setting	Population-based setting in Germany. Health insurance perspective	Base case—5yr LDCT screening. Tested 76 scenarios based on age (starting and quitting smoking), smoking history (yrs/time since quit) and nodule status (Nelson and NLST)	Natural history modules for cancer detection, treatment and survival—includes NLST and NELSON data/guidelines for screening and nodule management	Life-years. Benefits: cancers detected at early stage; reduction in LC mortality; LC deaths averted. Harms: interval cancer cases; overdiagnosis	Life-years. Costs included LDCT exams, staging tests and lifetime treatment. Costs were based on British healthcare exposure, to which German prices were applied	Cost-effectiveness was represented by average and incremental cost per life-years gained (LYG) and averted lung cancer deaths	Microsimulation. Structural modules: population, natural history, clinical detection, survival, screening and life history	Lifetime; equal (3%) and differential (3% for costs and 1.5% for LYG) annual discounting

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
Tomonaga et al. 2018(171)	Estimate the cost-effectiveness of LDCT screening	Population-based setting in Switzerland. Costs were analysed from a Swiss healthcare system perspective (University Hospital Zurich)	648 screening scenarios with different screening start and stop ages, smoking eligibility criteria, and screening intervals across a lifetime horizon in a cohort born 1935–1965	Applied the MISCAN microsimulation model to estimate the natural history of LC and potential impact of LDCT screening compared with no screening. 324 NLST-like and 324 NELSON-like scenarios modelled	Percentage of the total population ever screened, LC incidence and mortality, life-years gained (LYG), CT examinations in the population, false positive CT screens, occurrence of overdiagnosis, non-LC related exams	In/out-patient episodes, including treatment costs (incl immunotherapy for n=74), overhead costs, i.e. capital costs, real estate and associated costs. Costs assigned to three phases: 1) initial treatment, 2) continued care, and 3) terminal care	Cost-effectiveness. Total costs and LYG of each scenario. ICER calculated as the incremental costs divided by the incremental LYG compared with the previous scenario	Microsimulation Screening Analysis-Lung (MISCAN) model was adapted using country-specific input parameters regarding LC epidemiology, smoking behaviours and treatment costs	Lifetime, 3% discount applied to both costs and effects

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
Wade et al. 2018(173)	Assess cost-effectiveness of LDCT screening in Australia	Australia; health system perspective	Base case. Three annual LDCT lung screens compared with those associated with usual care	Trial population and LC outcomes observed in the NLST were applied to Australian population-based survival rates with Australian cost estimates	Estimated life-years (LY) adjusted by an estimate of quality of life, to give an estimate of the QALYs. Utility values were obtained from the NLST	LDCT screen, direct medical costs involved in diagnostic follow-up, staging, treatment, clinician consults, treatment interventions, and hospitalisation (excluded infrastructure, staff and non-medical costs, GP consults before Dx). Base case ICERs: false positive disutility, screen cost, other-case mortality benefit LDCT,	Cost–utility analysis (cost per QALY) based on applying Australian cost and survival data to NLST observed outcomes	One-way sensitivity analyses were conducted on a range of values for (1) cost per screen; (2) cost of diagnostic follow-up for a false-positive result; and (3) cost of diagnosis, staging and treatment for LC. Probabilistic sensitivity analysis also conducted, allowing for acceptability curves to be plotted	10-year horizon. A discount rate of 5% (with sensitivity analyses from 0%–7%) was used both for costs and expected LYS

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
						incidental finding cost, false +ve follow-up cost, PPV of incidence scans, mean III/IV NSCLC cost, mean treatment cost			
Jaine et al. 2018(142)	1) Estimate the health gains, costs and cost-effectiveness of an LDCT screening program for LC in New Zealand 2) Determine the variables with the greatest	New Zealand health system perspective including population subgroups (Māori)	Modelled biennial LDCT screening applied to such a population over 20 years (2011–2031) among all estimated eligible New Zealanders alive in 2011	NLST results plus multiple sources including NZ census, NZ cancer registry, NLST, NZ Breast Screen registry, Toyoda 2008,(193) Humphrey 2013	QALYs—health utilities from the literature. Included short-term disutility (loss of QoL) due to indeterminate findings. Cases that did not have further cancer sequelae	Cost per person invited; LDCT; incidental finding; diagnostic tests (CT guided biopsy, bronchoscopy, EBUS); complications (hospital stay pneumothorax);	Cost-effectiveness was represented by incremental cost per QALYs	Markov microsimulation stage shift model (health states: healthy; lung cancer—local, regional, distant; dead—lung cancer, other cause)	Lifetime horizon for QALYs, discounted at 3% per annum

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
	influence on the cost-effectiveness of a lung cancer screening program 3) Determine variations in cost-effectiveness by population groups				returned to normal QoL	All cost in $NZ from 2011			
Yang et al. 2017(170)	Adjust lead-time bias and quality-of-life changes for estimating the cost-effectiveness of implementing CT screening in Taiwan	ICER from the public payer's perspective in Taiwan	Estimated quality-adjusted life expectancy (QALE), loss-of-QALE, and lifetime healthcare expenditures per case of LC stratified by	NLST data used to estimate the savings of loss-of-QALE and additional costs of lifetime healthcare expenditures after CT screening	QALE, loss-of-QALE, and lifetime healthcare expenditures per case of LC stratified by pathology and stage. The EuroQol five-dimension questionnaire	Lifetime healthcare expenditures per case calculated using National Health Insurance (NHI) expenditure incl out/inpatient expenditures, and those spent on diagnosis	CEA	Not stated	Lifetime, applied a 3% annual discount rate for calculation when the QALE values were employed in the estimation of ICER

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
			pathology and stage.	The difference in overall costs (i.e. incremental cost) divided by the savings of loss-of-QALE	(EQ-5D) was used to estimate the utility values of QoL	and treatments (excluding transportation costs, payments to caregivers and human capital loss)			
OTHER COST STUDIES									
Huo et al. 2019(73)	To determine the complication rates and downstream medical costs associated with invasive diagnostic procedures performed for identification of lung	US claims database of medical insurance claims	Not applicable—instead four groups of invasive diagnostic procedures considered, which are: cytology or needle biopsy; bronchoscopy; thoracic	Used an incremental approach by constructing a matched control cohort that did not undergo these invasive procedures	Complication rates	Estimated 1-year complication costs by aggregating insurance payments and out-of-pocket expenditures for inpatient, outpatient, and physician services using codes on diagnosis date	Estimated the 1-year complication costs by aggregating insurance payments and out-of-pocket expenditures for in/outpatient, and physician services based on ICD-9 codes;	N/A	N/A

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
	abnormalities in the community setting		surgery; and others			or procedure date or for complications.)	estimated the mean procedure costs for each invasive diagnostic procedure group		
Chung et al. 2019(175)	Study presents a profitability analysis of a LC screening program using broader NCCN criteria (includes additional risk factors)	Under-served community in south-eastern US (Georgia Cancer Center and the Department of Radiology and Imaging at Augusta University Medical Center)	Real-life screening strategy of NCCN high-risk screening (55–74 years, current or former smoker, quit last 15 years; 30 PYH; one additional risk factor); used PET/CT scanning in off-service hour	Cost, direct cost and adjusted net margin per case after factoring downstream revenue from positive scans and other findings	Not reported but clinical data for lung ca dx reported as 20 cases, of which 73.7% were early stage (I to IIB)	The mean overhead cost over total cost was 42.3%	Direct cost components incl payroll and benefits, drugs and pharma agents, and wages. Indirect costs incl admin fees, machine depreciation, department support, facilities, technology and telecoms, supplies, patient support,	N/A	N/A

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
							purchased services, repairs and maintenance		
Kumar et al. 2018(169)	To quantify the value of risk-targeted selection for lung cancer screening compared to National Lung Screening Trial (NLST) eligibility criteria	US healthcare sector with the target population of current and former smokers eligible for screening	Jointly estimates the baseline hazards and the effects of risk factors on four transitions between the four health states	NLST (which compared LDCT with CXR)	Incremental 7-year mortality, life-expectancy, quality adjusted life years (QALY), costs and cost-effectiveness of screening with LDCT vs chest X-ray at each decile of lung cancer mortality risk	Costs included initial screening; medical care use including diagnosis and management following a positive screening result; and age-stratified background medical costs	Cost-effectiveness analysis using multi-state prediction model using ICER and incremental net monetary benefit (iNMB)	Applied a novel multi-state regression model to predict health state transitions as a function of an individual participant's baseline characteristics and either LDCT or CXR. Four health states: 1) alive without cancer; 2) alive with LC; 3) dead due to other	Lifetime, with all future life-years and costs discounted at 3%

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
								causes; or 4) dead due to LC	
Hinde et al. 2018(194)	To expand on the existing pool of cost-effectiveness studies by evaluating the results of the recently conducted community based LHC (Lung Health Check) screening pilot in deprived areas of Manchester	Manchester, England; community venues; a NHS and PSS perspective taken on costs and population health	UKLS method—ever-smokers screened at GP and those with 6-year lung cancer risk of at least 1.51% offered annual LDCT	Apply UKLS estimates. Stage & intervention proportions for true positives applied from Cancer Research UK (CRUK), alongside estimates of stage distribution, either from the pilot (immediate diagnosis at screen) or from an estimate of the stage distribution of the population without the program, here using Office of	Estimated life-years (LY) adjusted by an estimate of quality of life, to give an estimate of the QALYs	Three main cost factors: 1) cost of conducting the program; 2) cost implications of diagnosing and treating a true +ve, and those of diagnosing a false +ve; 3) local reference costs rather than national costs (exclude the non-recurrent project costs of setting up the pilot; include detailed costing	CUA (QALYs)	UKLS method; decision analytic	All costs and benefits are discounted at a rate of 3.5% per year over a lifetime analysis

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
				National Statistics (ONS) data, to inform later diagnosis		for diagnostic work-up of LC)			
Gareen et al. 2018(174)	Determine the comparative costs across the NLST LDCT and CXR arms, and the impact of significant incidental findings (SIFs) on that comparison. Goal to examine the downstream costs associated with LDCT screening	NLST participants aged 65 years and older. Data obtained through linkage with Medicare administrative billing data based on social security number (SSN)	Not reported	Not reported	Not reported	Medicare fee-for-service claims data, both total costs and radiological costs following LDCT and CXR screening. Annual costs estimated using outpatient procedures and hospitalisations (excluded LDCT and CXR costs, as borne by trial and not billed to Medicare)	Not reported	Not reported	Not reported

Study, pub year	Study aim	Setting & perspective	Screening strategies tested	Source of effectiveness estimates	Definition & measurement of health outcomes	Definition & measurement of health costs (type of costs included)	Economic evaluation method applied (CEA, CUA)	Type of model (decision analytic, Markov model, etc)	Time horizon & discount rate
Marshall et al. 2019(176)	To describe the first direct medical costs associated with LDCT screening in Australia (Queensland Lung Cancer Screening Study—QLCSS)	Healthcare perspective, therefore only describe direct medical costs	Modified NLST, ACRIN eligibility criteria and nodule management. 3 annual CT screens and up to 5 years follow-up	Cost–benefit analysis, mean per-person cost, inflated to 2017 AUD$	Descriptive statistics only due to the small size of the cohort and low number of cancer-positive participants (14 over 5 years)	Direct medical costs: diagnostic work-up diagnostic procedures, staging, clinician consultations, treatment interventions and hospitalisation	CEA	N/A	N/A

Table 11b: A summary of cost-effectiveness studies—continued

Study, year of publication	Base-case findings (the ICER)	Results from sensitivity and scenario analyses	Cost-effective	Comments
MICROSIMULATION				
Toumazis et al. 2019(172)	Base-case analysis, assuming 4% short-term disutility results in only biennial strategies being cost-effective at a threshold of US$100,000/QALY (strategy B-50-70-40-10 produced the highest QALY gain of those strategies, with an ICER of US$92,561)	Results of sensitivity analyses show the ICER was most sensitive to the assumed disutility of the indeterminate disutility factor, the discount rate and the utility value applied to early stage lung cancer	The authors conclude that with a stated threshold of at least US$100,000 per QALY (as the willingness to pay), there are some annual strategies that are cost-effective (assuming no disutility of indeterminate findings) and only biennial strategies (assuming a 4% disutility). Strategies would only be considered cost-effective at US$50,000 threshold assuming no disutility of indeterminate findings	The QALY gains per individual are very low, particularly as these are over a lifetime—a gain of 0.0090 for B-50-70-40-10 is questionable
Treskova et al, 2017(71)	Base case of 5-year LDCT annual lung screening program: The most cost-effective scenario yielded an ICER of €16,754/LYG (this was the strategy 55-74-40-10, with the NELSON-like nodule management protocol, with assessment of volume-doubling time 3 months after the initial screening as a sole predictor of malignancy)	The drivers of cost-effectiveness were the cost per CT exam, treatment costs and lung cancer long-term survival probability in screening	Analysis shows nodule management programs influence the cost-effectiveness of lung cancer screening; the paper does not set a threshold for what is considered cost-effective, but states their values are within what has been reported by others as cost-effective	Study intended to outline and discuss efficient scenarios rather than provide solid recommendations. Challenge is that outcomes have been reported with various end points—LYG, deaths averted, etc—which complicates interpretation

Study, year of publication	Base-case findings (the ICER)	Results from sensitivity and scenario analyses	Cost-effective	Comments
Tomonaga et al. 2018(171)	Compared with no screening, the analysed scenarios cost between €24,972 and €48,369 per LYG. Assuming a QALY to LYG proportion of 0.70, the scenarios would cost between €35,674 and €69,099 per QALY. All showed a cost-effectiveness ratio below €50,000 per LYG (≈€70,000 per QALY). Results showed screening most cost-effective for strategies for smokers or ex-smokers who smoked more than 30 years, at least 15 cigarettes per day and had ceased less than 10 years ago. Annual screening of high-intensity smokers appeared most efficient	The sensitivity analyses conducted using the USPSTF scenario and the most promising NLST-like and NELSON-like scenarios as base cases showed CT costs, LC treatment costs and attendance rate had a modest influence on the cost-effectiveness of screening. After weighting the costs of the USPSTF base-case scenario, the ICERs versus no screening increased from €36,953 to €38,857 per LYG (+4%)	Authors estimated the cost-effectiveness to be better than €50,000 per LYG (or €70,000 per QALY) for all assessed screening scenarios (may be cost-effective in a high-income, central European country). Different smoking eligibility criteria (NLST-like or NELSON-like) for selecting the population to be screened showed comparable results	Cost-effectiveness was highly dependent on screening intervals and smoking eligibility criteria: lung cancer screening was generally less costly when performed less frequently and when restricted to high-risk individuals. Despite annual screening being more expensive than biennial and triennial screening, annual screening showed the greatest potential reduction in LC mortality and the highest increase of LYG
Wade et al. 2018(173)	The corresponding ICERs were AU$138,000 (80% CI: AU$84,700–AU$353,000) per LY gained and AU$233,000 (80% CI: AU$128,000–AU$1,110,000) per QALY gained. The ICERs by current and former smoking status were AU$123,000 and AU$1,480,000 per QALY gained, respectively	The variation in base-case parameters resulted in ICER estimations that varied from AU$127,000 to AU$509,000 per QALY gained for the combined population. The highest ICER observed in sensitivity analyses was when a 2-month disutility weighting for false-positive scan results was included, resulting in an ICER of AU$509,000/QALY gained (this	A threshold analysis for the cost of an LDCT screen demonstrated that even at very low screening costs, lung screening would not be cost-effective under the base-case assumptions tested	The authors note that it's important that future economic evaluations consider alternative screening eligibility criteria, intervals, nodule management, the impact and costs of new therapies, investigations of incidental findings, and incorporation of smoking cessation interventions

Study, year of publication	Base-case findings (the ICER)	Results from sensitivity and scenario analyses	Cost-effective	Comments
		would be even higher if restricted to the past-smoker population)		
Jaine et al. 2018(142)	The overall ICER was US$104,000 per QALY gained (95% UI US$59,000–US$175,000	Sensitivity and specificity of the CT screening test for the base case were those reported in the NLST (sensitivity 93.8%, specificity 73.4%). ICER most sensitive to assumptions on proportion never screened (and therefore to cost of screening), incidence of LC and test specificity	Not cost-effective across the whole population as the ICER was NZ$154,000 per QALY gained (US$104,000 per QALY). Plus, the screening program incurred direct intervention costs that exceeded any cost savings due to less severe disease at diagnosis, with an increased net total cost of NZ$285 million (US$192 million). However, the intervention was more cost effective for Māori compared with non-Māori, where the ICER was NZ$101,000 per QALY gained (95% UI NZ$62,000–NZ$162,000)	Cost-effectiveness varied moderately by socio-demographics, with the 'best' ICER being US$52,000 for 70–74-year-old Māori females and the 'worst' ICER being US$142,000 for 55–59-year-old non-Māori females. The ICER varied little by smoking status, due to higher competing mortality risk limiting QALY gains for current smokers. Important to note that the estimate of quality of life applied used disability weights from the global burden of disease project and not preference-based utility measures; these are not equivalent to applying utility values and should be interpreted with caution as representing QALYs

Study, year of publication	Base-case findings (the ICER)	Results from sensitivity and scenario analyses	Cost-effective	Comments
Yang et al. 2017(170)	ICER = US$22,755 per person. After dividing this by savings of loss-of-QALE (1.16 (QALY)), the ICER was US$19,683 per QALY, reducing to US$10,947 per QALY if NELSON stage distribution for CT screening was used	The sensitivity analysis of varying parameter values of uncertainties seems to show consistently an ICER of about 1 gross domestic product (GDP) (US$20,925) per capita per QALY	LDCT screening for LC among high-risk smokers would be cost-effective in Taiwan	
OTHER COST STUDIES				
Huo et al. 2019(73)	The mean incremental complication costs were $6320 (95% CI, $5863–$6777) for minor complications to $56,845 (95% CI, $47,953–$65,737) for major complications	The estimated complication rate was 22.2% (95% CI, 21.7%—22.7%) for individuals in the young age group and 23.8% (95% CI, 23.0%—24.6%) for those in the Medicare group	Not reported	The rates of complications after invasive diagnostic procedures were higher than the rates reported in clinical trials
Chung et al. 2019(175)	The adjusted net margin per case was –$212 in the first year but turned positive to $177 in the third fiscal year. The total break-even point of adjusted net margin was between 6% and 7% of indirect cost as a function of charges	Of the 60 new patients introduced to the hospital system, a gross margin per case of $211 was found	Free lung cancer screening can demonstrate profitability from downstream revenue with a lag time of 2 years	

Study, year of publication	Base-case findings (the ICER)	Results from sensitivity and scenario analyses	Cost-effective	Comments
Kumar et al. 2018(169)	The incremental cost-effectiveness ratio (ICER) was $US60,000/QALY; it was similar across risk deciles ($75,000/QALY (lowest risk decile) to $53,000/QALY (highest risk decile)). Payers willing to pay $100,000/QALY would pay for LDCT screening for all decile groups	Assessed the influence of alternative assumptions on the model-projected cost-effectiveness: 1) LDCT provides continually accruing lung cancer mortality gains by extrapolating the reduced hazard of lung cancer mortality throughout the patient's lifetime; 2) Removal of age-specific background medical costs; 3) Assign utility weights of 0.57 or 1.0 following a diagnosis of lung cancer (base case=0.77) Alternative assumptions did not substantially alter the findings	While risk-targeting can improve screening efficiency in terms of early lung cancer mortality per person screened, the gains in efficiency are attenuated and modest in terms of life years, QALYs and cost-effectiveness	Also calculated the incremental net monetary benefit (iNMB) for each participant to summarise the value of a risk-stratified screening strategy compared with the NLST inclusion criteria at common willingness to pay (WTP) thresholds of $50,000/QALY and $100,000/QALY
Hinde et al. 2018(194)	ICER of £10,069/QALY	Explored the sensitivity of the model to the CT mortality rates by adjusting the estimated time dependent rates using a hazard ratio. This found that applying a hazard ratio of 0.5 (i.e. reducing the annual mortality rate for CT-detected patients by half) reduced the ICER to £5,801/QALY. Similarly a hazard ratio of 1.5 resulted in an ICER of £26,837. Also, by reduced lead times estimates to 3, 2, 1 and 0 years for stage 1–4 respectively	ICER below any of the threshold values considered appropriate (£20,000 to £30,000/QALY, but authors argued it should be closer to £13,000/QALY), therefore suggesting that, under the base-case assumptions, the Manchester pilot represents a cost-effective use of NHS resources	Lead times would need to increase to 8.0, 5.4 and 2.7 for the screening program to no longer be cost effective (assuming the same relative size of the lead times). It is important to note that the strategy tested in this analysis is restricted to ever-smokers at high risk (which supports analyses in other papers on which strategies are likely to be most cost-effective)

Study, year of publication	Base-case findings (the ICER)	Results from sensitivity and scenario analyses	Cost-effective	Comments
		reduces the ICER to £5,579/QALY as the benefits of diagnosing a LC earlier increase		
Gareen et al. 2018(174)			The adjusted annual mean total per person costs were not significantly different between screening arms (LDCT: $11,029 [95% CI: $10,107, $11,951]; CXR:$10,905 [95% CI: $10,059, $11,751]), despite higher proportions of individuals with significant incidental findings (SIFs) in the LDCT vs. the CXR arm (18% vs. 4%, p <.0001)	
Marshall 2019(176)	Average total direct medical cost per participant was AUD3768. Average direct medical cost of surgery was AUD22,659. Average non-surgical cost was AUD47,395 (radiotherapy, chemotherapy, palliative care)	Estimated costs of treatment and follow-up for 14 cancers had screening not taken place. Overall costs for treatment would be similar for screening and clinical presentation, but outcome for the patients would have been much worse	QLCSS cost data similar to NLST results and suggest that screening could limit treatment cost and improve outcomes	Small sample size and did not include indirect medical costs

Appendix 1

PICO statement

Types of studies to be included

Randomised and non-randomised studies of interventions that investigate low-dose computed tomography (LDCT) lung cancer screening.

Condition or domain being studied

Lung cancer

Participants/population

Individuals with a high risk of lung cancer

Definition of high-risk population:

NLST example: Aged 55–74 years with ≥30 pack-years smoking history and who have quit within the past 15 years

Types of intervention/exposure

Any intervention, program or trial designed to test the effectiveness, harms, cost-effectiveness of major components of LDCT screening in a high-risk population

Comparator(s)/control

For RCTs: No intervention (or CXR in some intervention studies). For studies that report program evaluation, acceptability, feasibility or service outcomes (e.g. timeliness, equity), no comparator is required.

Primary outcome(s)

Effectiveness of lung cancer screening

Harms of lung cancer screening

Program components of lung cancer screening

Cost-effectiveness and cost analysis of lung cancer screening

Appendix 2

Search strategy by database

DATABASE: MEDLINE (OVID)

Lung cancer	1. Exp Lung Neoplasms/ or (exp neoplasms and (lung/) 2. (NSCLC or NSLC or SCLC or SLC).tw,ti,ab,ot,kw. 3. (lung adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or metast* or adeno* or small cell or squamous)).tw. 4. (pulmon* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or metast* or adeno* or small cell or squamous)).tw. 5. 1 OR 2 OR 3 OR 4
Screening	6. exp mass screening/ 7. screen*.ti,ab. 8. Mass Screening/ae, mo 9. 6 OR 7 OR 8
Low dose computed tomography	10. exp Tomography, X-Ray Computed/ 11. ((CT or CAT) adj3 (scan$ or screen$)).ti,ab,ot,kw. 12. ((comput$ adj3 tomogra$) and (scan$ or screen$)).ti,ab,ot,kw. 13. (tomogra$ or helix or helical or spiral$ or spiro$ or axial).ti,ab,ot,kw. 14. 10 OR 11 OR 12 OR 13 15. ((low$ adj3 dos$) or LDCT).ti,ab,kw,ot. 16. (ultralow$ or ultra-low$) adj3 dos$).ti,ab,kw,ot. 17. (low-dos$ or ultralow-dos$).ti,ab,kw,ot. 18. 15 OR 16 OR 17 19. 14 AND 18
Combine	20. 5 AND 9 AND 19
Effectiveness	21. Effectiveness. tw. 22. Randomized controlled trial or randomised controlled trial).pt. 23. Controlled clinical trial.pt. 24. (Randomized or randomised).ab. 25. 21 OR 22 OR 23 OR 24 26. 20 AND 25
Harms	27. (adverse or undesirable or harm* or serious) adj3 (effect? or reaction? or event? or outcome?)).tw. 28. harm?.tw. 29. (overdiagnosis or over diagnosis or over-diagnosis or over detection or overdetection or over-detection or overtreatment or over treatment or over-treatment).tw. 30. Mortality/ 31. adverse.tw. 32. (unnecessary adj3 treatment?).tw. 33. (unnecessary adj3 procedures?).tw. 34. 227 OR 8 OR 29 OR 30 OR 31 OR 32 OR 33 35. exp anxiety/

	36. exp depression/ 37. exp Quality of life/ 38. exp stress, psychological/ 39. (psycho* adj3 (consequence* or harm* or distress*)).tw. 40. 35 OR 36 OR 37 OR 38 OR 39 41. 34 AND 40 42. 20 AND 41
Main components of trials, programs and pilot studies	43. exp Organizational Innovation/ 44. Preventive Health Services/mt,og,st [Methods, Organization & Administration, Standards] 45. Primary Health Care/mt,og [Methods, Organization & Administration] 46. Program Evaluation/ 47. Exp Implementation Science/ 48. Exp Pilot projects/ 49. (implement* or evaluat*).ti,ab,ot. 50. 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 51. exp Smoking cessation/ 52. exp smoking reduction/ 53. Treatment adherence and compliance.tw. 54. 51 OR 52 OR 53 55. 50 AND 54 56. 20 AND 55
Cost-effectiveness	57. exp Economics/ 58. Economics, Medical/ 59. Economics, Nursing/ 60. Economics, Pharmaceutical/ 61. exp Economics, Hospital/ 62. (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. 63. 57 OR 58 OR 59 OR 60 OR 61 OR 62 64. exp "Costs and Cost Analysis"/ 65. exp Health Care Costs/ 66. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. 67. (value adj2 (money or monetary)).ti,ab,kf. 68. 64 OR 65 OR 66 OR 67 69. 63 AND 68 70. 20 AND 69
Limits	English language, Humans, Publication date: 2009 - current

DATABASE: PSYCINFO (OVID)

Lung cancer	1. (exp Neoplasms/) AND (exp Lung/) 2. (NSCLC or NSLC or SCLC or SLC).tw,ti,ab,ot,kw. 3. (lung adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or metast* or adeno* or small cell or squamous)).tw. 4. (pulmon* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or metast* or adeno* or small cell or squamous)).tw. 5. 1 OR 2 OR 3 OR 4
Screening	6. screen*.ti,ab. 7. exp screening/ 8. 6 OR 7
Low dose computed tomography	9. ((CT or CAT) adj3 (scan$ or screen$)).ti,ab,ot,kw. 10. ((comput$ adj3 tomogra$) and (scan$ or screen$)).ti,ab,ot,kw. 11. (tomogra$ or helix or helical or spiral$ or spiro$ or axial).ti,ab,ot,kw. 12. exp Tomography/ 13. 9 OR 10 OR 11 OR 12 14. ((low$ adj3 dos$) or LDCT).ti,ab,kw,ot. 15. ((ultralow$ or ultra-low$) adj3 dos$).ti,ab,kw,ot. 16. (low-dos$ or ultralow-dos$).ti,ab,kw,ot. 17. 14 OR 15 OR 16 18. 13 AND 17
Combine	19. 5 AND 8 AND 18
Effectiveness	20. Effectiveness.tw. 21. (Randomized or randomised).ab. 22. exp clinical trial/ 23. 20 OR 21 OR 22 24. 19 AND 23
Harms	25. (adverse or undesirable or harm* or serious) adj3 (effect? or reaction? or event? or outcome?)).tw. 26. harm?.tw 27. (overdiagnosis or over diagnosis or over-diagnosis or over detection or overdetection or over-detection or overtreatment or over treatment or over-treatment).tw. 28. Mortality/ 29. adverse.tw. 30. (unnecessary adj3 treatment?).tw. 31. (unnecessary adj3 procedures?).tw. 32. 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 33. exp anxiety/ 34. exp depression/ 35. exp Quality of life/ 36. (psycho* adj3 (consequence* or harm* or distress*)).tw. 37. exp Psychological Stress/ 38. 33 OR 34 OR 35 OR 36 OR 37 39. 19 AND 32

	40. 19 AND 38
Main components of trials, programs and pilot studies	41. exp Organizational Innovation/ 42. preventative health/ health behaviour or Health care services or prevention or health promotion or health or health education or intervention 43. (implement* or evaluat*).ti,ab,ot. 44. exp Program Evaluation/ 45. 41 OR 42 OR 43 OR 44 46. exp Smoking cessation/ 47. Treatment adherence and compliance.tw. 48. Tobacco smoking 49. 46 OR 47 OR 48 50. 19 AND 45 51. 19 AND 49
Cost-effectiveness	52. exp Economics/ 53. (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. 54. 52 OR 53 55. exp "Costs and Cost Analysis"/ 56. exp Health Care Costs/ 57. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. 58. (value adj2 (money or monetary)).ti,ab,kf. 59. 55 OR 56 OR 57 OR 58 60. 54 AND 59 61. 19 AND 60
Limits	English language, Humans, Publication date: 2009 - current

DATABASE: EMBASE (OVID)

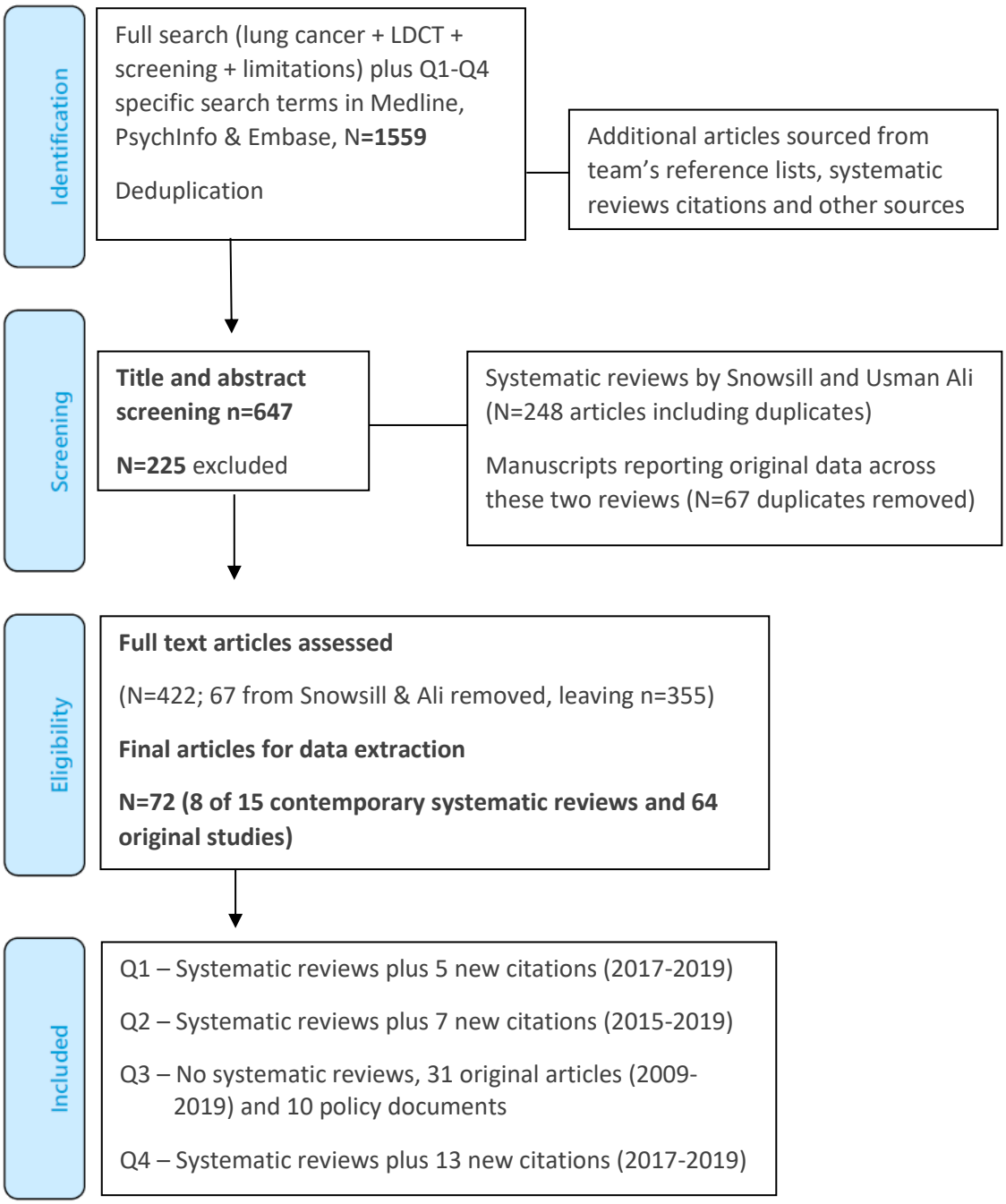
Lung cancer	1. Exp Lung Neoplasms/ or (exp neoplasms and (lung/) 2. (NSCLC or NSLC or SCLC or SLC).tw,ti,ab,ot,kw. 3. (lung adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or metast* or adeno* or small cell or squamous)).tw. 4. (pulmon* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or metast* or adeno* or small cell or squamous)).tw. 5. 1 OR 2 OR 3 OR 4
Screening	6. exp mass screening/ 7. screen*.ti,ab. 8. 6 OR 7
Low dose computed tomography	9. exp Tomography, X-Ray Computed/ 10. ((CT or CAT) adj3 (scan$ or screen$)).ti,ab,ot,kw. 11. ((comput$ adj3 tomogra$) and (scan$ or screen$)).ti,ab,ot,kw. 12. (tomogra$ or helix or helical or spiral$ or spiro$ or axial).ti,ab,ot,kw.

	13. 9 OR 10 OR 11 OR 12 14. ((low$ adj3 dos$) or LDCT).ti,ab,kw,ot. 15. ((ultralow$ or ultra-low$) adj3 dos$).ti,ab,kw,ot. 16. (low-dos$ or ultralow-dos$).ti,ab,kw,ot. 17. 14 OR 15 OR 16 18. 13 AND 17
Combine	19. 5 AND 8 AND 18
Effectiveness	20. Effectiveness.tw. 21. (Randomized or randomised).ab. 22. exp clinical trial/ 23. 20 OR 21 OR 22 24. 19 AND 23
Harms	25. (adverse or undesirable or harm* or serious) adj3 (effect? or reaction? or event? or outcome?)).tw. 26. harm?.tw. 27. (overdiagnosis or over diagnosis or over-diagnosis or over detection or overdetection or over-detection or overtreatment or over treatment or over-treatment).tw. 28. Mortality/ 29. adverse.tw. 30. (unnecessary adj3 treatment?).tw. 31. (unnecessary adj3 procedures?).tw. 32. 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 33. exp anxiety/ 34. exp depression/ 35. exp Quality of life/ 36. exp stress, psychological/ 37. (psycho* adj3 (consequence* or harm* or distress*)).tw. 38. 33 OR 34 OR 35 OR 36 OR 37 39. 32 AND 38 40. 19 AND 39
Main components of trials, programs and pilot studies	41. exp Organizational Innovation/ 42. Preventive Health/Preventative health service, major clinical study, health education, health promotion, health behaviour 43. Program Evaluation/ 44. Exp Pilot projects/ 45. (implement* or evaluat*).ti,ab,ot. 46. 41 OR 42 OR 43 OR 44 OR 45 47. exp Smoking cessation/ 48. exp smoking reduction/ 49. Treatment adherence and compliance.tw. 50. 47 OR 48 OR 49 51. 46 AND 50 52. 19 AND 51

Cost-effectiveness	53. exp Economics/ 54. Economics, Medical/ 55. Economics, Nursing/ 56. Economics, Pharmaceutical/ 57. exp Economics, Hospital/ 58. 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. 59. 53 OR 54 OR 55 OR 56 OR 57 OR 58 60. exp "Costs and Cost Analysis"/ 61. exp Health Care Costs/ 62. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. 63. (value adj2 (money or monetary)).ti,ab,kf. 64. 60 OR 61 OR 62 OR 63 65. 59 AND 64 66. 19 AND 65
Limits	English language, Humans, Publication date: 2009 – current

Appendix 3

PRISMA flowchart of the literature selection process is included



Appendix 4

Quality ratings for Question 3 and Question 4

Author (date)	Brief description	Quality tool used (EPHPP, CASP or CHEERS)	Overall rating
Ahmed 2018(105)	Evaluation of LDCT lung cancer screening program at single site in Florida	EPHPP	Moderate
Begnaud 2016(103)	Evaluation (descriptive) of single institution experience of screening program (University of Minnesota Health)	CASP	Low
Begnaud 2017(147)	Pilot study of lung cancer screening promotion program (University of Minnesota Heath)	CASP	Moderate
Black 2018(148)	Implementation of nurse practitioner program at a single institution (University of Maryland Medical Center)	CASP	Low
Brenner 2018(106)	Pilot study of lung cancer screening program using Quality Improvement methodology; single institute study (large academic primary care practice in North Carolina)	CASP	Moderate
Brenner 2019(159)	A qualitative content analysis of SDM consultations	CASP	Low
Cardarelli et al. 2017(146)	Campaign effectiveness; community-engaged approach. Campaign, known as the Terminate Lung Cancer (TLC) program, based on community awareness of screening and rates of LDCT orders across two targeted Eastern Kentucky regions	EPHPP	Moderate
Catteneo 2018(107)	Retrospective audit of the first five years of a lung cancer screening program	EPHPP	Low
Crosbie 2018(115)	UK Lung Health Check baseline results	EPHPP	Moderate
Crosbie 2019(75)	UK Lung Health Check second round results	EPHPP	Moderate
Cole 2019(125)	Cross-sectional study to assess accuracy of EHR data to identify potential patients for LDCT (community-based healthcare system in the Pacific Northwest, US)	EPHPP	Low

Author (date)	Brief description	Quality tool used (EPHPP, CASP or CHEERS)	Overall rating
Copeland 2019(118)	Survey of lung cancer screening centres to assess implementation	CASP	Moderate
Fabbrini 2018(108)	Initial results of lung cancer screening program	EPHPP	Moderate
Gesthalter 2017(114)	Qualitative evaluation of LDCT program	CASP	High
Gould 2017(113)	LDCT program characteristics and data collection approaches	CASP	Moderate
Jessup et al 2018(156)	Campaign effectiveness and education	EPHPP	Moderate
Kinsinger 2017(112)	Evaluation of 8 centres in the Veterans Health Administration (VHA)	EPHPP	High
Lanni 2018(109)	Single-institution evaluation of a one-year screening program	EPHPP	Low
Lee 2018(150)	Evaluation of Korean Lung Cancer Screening pilot study	EPHPP	Moderate
Li 2018(155)	Assess referrals for LDCT screening and identify facilitators and barriers to adoption following recent policy changes	EPHPP	High
Lillie 2017(119)	Survey study to determine factors important to patients in LDCT screening SDM	EPHPP	Moderate
Marcus 2012(117)	To report on the methods used to recruit participants to the NLST	EPHPP	Moderate
McKee 2013(102)	Description of free CT-screening program in the US setting	EPHPP	Moderate
Modin 2017(122)	Retrospective analysis of EHR vs. SDM conversation for eligibility determination (five-hospital program, Seattle, Washington)	EPHPP	High
O'Brien 2017[125]	Comparative study of electronic vs. paper form for LDCT eligibility pre-screening	EPHPP	Moderate
Okereke 2016(104)	Single institution evaluation of a one-year screening program	EPHPP	Low
Qiu 2016(117)	Survey and interview study on characteristics and implementation barriers in LDCT programs	EPHPP	Moderate
Ruparel 2019(141)	Randomised controlled trial nested within the LSUT study that aims to evaluate the impact of a novel information film on	EPHPP	High

Author (date)	Brief description	Quality tool used (EPHPP, CASP or CHEERS)	Overall rating
	informed decision-making for individuals considering participating in LDCT screening		
Shields 2019(111)	Observational cohort study to evaluate two years of LDCT screening program in single institution in Kentucky	EPHPP	Moderate
Springer 2018(157)	Description of campaign implementation in Michigan	CASP	Moderate
Strong 2018(110)	Description on the role of the nurse practitioner in screening programs	CASP	Low
Q4			
Toumazis 2019(172)	Assess the cost-effectiveness of LDCT after incorporating the Lung-RADS guidelines to manage indeterminate findings for the US population	CHEERS	High
Treskova 2017(71)	Investigate the effects of eligibility criteria and nodule management on the benefits, harms and cost-effectiveness of LS with LDCT in a population-based setting	CHEERS	High
Tomonaga 2018(171)	Estimate the cost-effectiveness of LDCT screening	CHEERS	High
Wade 2018(173)	Assess cost-effectiveness of LDCT screening in Australia	CHEERS	High
Jaine 2018(142)	1) Estimate the health gains, costs and cost-effectiveness of an LDCT screening program for LC in New Zealand 2) Determine the variables with the greatest influence on the cost-effectiveness of a lung cancer screening program 3) Determine variations in cost-effectiveness by population groups	CHEERS	Moderate
Yang 2017(170)	Adjust lead-time bias and quality-of-life changes for estimating the cost-effectiveness of implementing CT screening in Taiwan	CHEERS	Moderate
Huo 2019(73)	To determine the complication rates and downstream medical costs associated with invasive diagnostic procedures performed for identification of lung abnormalities in the community setting	CHEERS	Moderate

Author (date)	Brief description	Quality tool used (EPHPP, CASP or CHEERS)	Overall rating
Chung 2019(175)	Study presents a profitability analysis of a LC screening program using broader NCCN criteria (includes additional risk factors)	CHEERS	Moderate
Kumar 2018(169)	To quantify the value of risk-targeted selection for lung cancer screening compared with National Lung Screening Trial (NLST) eligibility criteria	CHEERS	Moderate
Hinde 2018(194)	To expand on the existing pool of cost-effectiveness studies by evaluating the results of the recently conducted community based LHC (Lung Health Check) screening pilot in deprived areas of Manchester	CHEERS	Moderate
Gareen 2018(174)	Determine the comparative costs across the NLST's LDCT and CXR arms, and the impact of significant incidental findings (SIFs) on that comparison. Goal to examine the downstream costs associated with LDCT screening	CHEERS	Low
Marshall 2019(176)	To describe the first direct medical costs associated with LDCT in Australia (Queensland Lung Cancer Screening Study—QLCSS)	CHEERS	Moderate