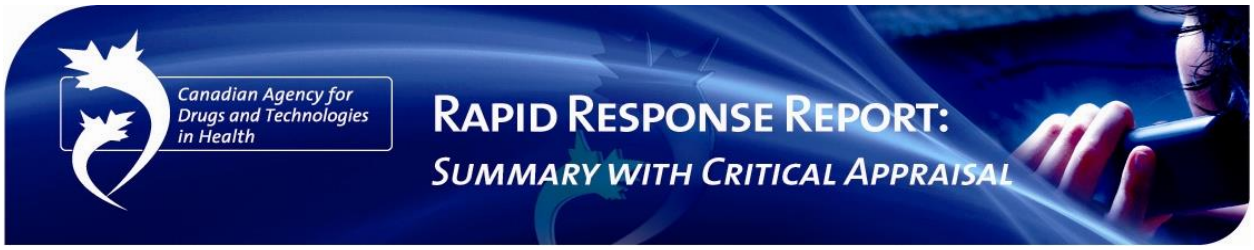

TITLE: Low-Dose Computed Tomography for Lung Cancer Screening: A Review of the Clinical Effectiveness, Diagnostic Accuracy, Cost-Effectiveness, and Guidelines

DATE: 22 September 2015

CONTEXT AND POLICY ISSUES

Lung cancer is the leading cause of cancer-related deaths, worldwide.[1,2] Complex interactions between genetic, hormonal, behavioural, and environmental factors play a role in the development of lung cancer.[3] Smoking is a major risk factor for lung cancer and accounts for 80% of the lung cancers in men and at least 50% of the lung cancers in women, worldwide.[3] It is estimated that in 2015, 26,600 Canadians will be diagnosed with lung cancer which represents 14% of all new cancers detected[4] and that 20,900 Canadians will die from lung cancer, which represents 27% of all cancer deaths in Canada in 2015.[4] In Canada, the 5-year survival rate for lung cancer patients is 14% and is considerably lower compared with 5-year survival rate for other cancers such as 95% for prostate cancer, 88% for breast cancer, and 65% for colorectal cancer.[3] A contributor to the lower survival rate is the fact that lung cancer is generally diagnosed at an advanced stage when patients present with symptoms and when cure by surgery is unlikely.[2,3] Screening strategies enabling detection of lung cancer at an early stage could potentially lead to decreased mortality.[2] Screening strategies for lung cancer include conventional radiography, sputum cytology, and the more recent low-dose computed tomography (LDCT). Results with conventional radiography and sputum cytology have been shown to detect slightly more early-stage lung cancers, though this was not accompanied by a reduction in advanced lung cancer detection and did not lead to a reduction in mortality.[5,6] A large randomized controlled trial, the National Lung Cancer Screening Trial (NLST) showed that with LDCT screening, a 20% reduction in mortality was achieved.[7] However, the false-positive rate is high for screening with LDCT and this can lead to harm due to unnecessary workups of benign nodules. Hence there is debate regarding the use of LDCT for lung cancer screening.

The purpose of this report is to review the clinical effectiveness and safety, diagnostic accuracy, cost-effectiveness, and evidence-based guidelines on the use of LDCT for lung cancer screening.

RESEARCH QUESTIONS

1. What is the diagnostic accuracy of low-dose computed tomography for lung cancer screening in high-risk populations?

2. What is the clinical effectiveness and safety of low-dose computed tomography for lung cancer screening in high-risk populations?

3. What is the cost-effectiveness of low-dose computed tomography for lung cancer screening in high-risk populations?

4. What are the evidence-based guidelines regarding the use of low-dose computed tomography for lung cancer screening?

KEY FINDINGS

The sensitivity and specificity with low-dose computed tomography (LDCT) were, respectively, 93.8% and 73.4%. The positive predictive value ranged between 2.4% to 4.4%. The negative predictive value was 99.9%.

Screening with LDCT resulted in detection of early-stage lung cancers and reduced cancer-related mortality. However, the high rate of false positives can lead to harm from unnecessary work-up of benign nodules.

The incremental cost-effectiveness ratio (cost per QALY gained) for screening with LDCT varied between US$11,252 and US$795,685 in North American settings, depending on the scenario.

The evidence-based guidelines recommended, annual lung cancer screening with LDCT for people with a smoking history of at least 30 pack-years and who currently smoke or have quit within the last 15 years.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and August 24, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients at risk of lung cancer
Intervention	Low-dose computed tomography
Comparator	No screening, other screening methods
Outcomes	Q1: Diagnostic accuracy, sensitivity, specificity, false-positive rate, false negative rate Q2: Clinical benefit (detection of patients with lung cancer and appropriate treatment) Q3: Cost-effectiveness Q4: Guidelines and recommendations (e.g., frequency of screening, population)
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), observational studies, economic studies, and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 2010. Systematic reviews in which all studies already included in a more recent or comprehensive systematic review were excluded. Studies already included in a selected systematic review were excluded. Since a high volume of higher quality evidence (systematic reviews and RCTs) was identified at the first level of screening, observational studies were not considered for inclusion.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist[8] was used for health technology assessments and systematic reviews, the British Medical Journal checklist[9] for economic studies, and the AGREE II tool[10] for evidence-based guidelines.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 480 citations were identified in the literature search. Following screening of titles and abstracts, 430 citations were excluded and 50 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Of these 55 potentially relevant articles, 34 publications were excluded for various reasons, while 21 publications met the inclusion criteria and were included in this report. These 21 publications were comprised of one HTA,[3] three systematic reviews,[5,6,11] and one RCT (with relevant details in two publications[7,12]), seven economic studies[2,13-18] and five

guidelines (with relevant details in eight publications[19-26]). Though the selected RCT was included in the HTA and systematic reviews, it was also reported separately in this report because of additional outcomes reported, which were not available in the HTA or systematic reviews. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included health technology assessments (HTAs), systematic reviews (SRs), randomized controlled trials (RCTs), economic studies, and evidence-based guidelines are summarized below. Details are provided in Appendix 2 for HTA, systematic reviews and RCT, Appendices 3 and 4 for economic studies and Appendix 5 for evidence-based guidelines.

Health Technology Assessments

One relevant HTA report[3] on lung cancer screening with LDCT was identified. It was published from Canada in 2014. It included a systematic review of three systematic reviews, a cost-effectiveness analysis and a budget impact analysis. One systematic review included eight RCTs published between 2002 and 2012; three RCTs compared LDCT versus chest x-ray (CXR) and five RCTs compared LDCT versus no screening. One systematic review included four RCTs published between 2009 and 2012; one RCT compared LDCT with CXR and three RCTs compared LDCT with no screening. One systematic review included one RCT published in 2011, comparing LDCT with CXR.

Systematic review

Three relevant systematic reviews[5,6,11] of lung cancer screening with LDCT compared with CXR or no screening were identified. All included smokers and ex-smokers. One systematic review[5] was published from China in 2014. It included nine RCTs published between 2002 and 2012; four RCTs compared LDCT with CXR and five RCTs compared LDCT with no screening. It reported on mortality, cancer detection rate, and false-positive rate. One systematic review,[11] was published from the United Kingdom in 2014. It included 10 RCTs and six observational studies and reported on recall rate, detection rate and positive predictive value (PPV). One systematic review,[6] included eight RCTs(three RCTs compared LDCT with CXR and five RCTs compared LDCT with no screening) published between 2002 and 2012 and 13 observational studies and reported on mortality and nodule detection.

Randomized controlled trial

One RCT[7,12] (the NLST), examining screening with LDCT compared with CXR was published from the United States of America (USA) in 2011. It included 53,454 patients at high risk of lung cancer and in the age range 55 to 74 years. These patients had a history of at least 30 pack-years of cigarette smoking and were either current smokers or had been smokers within the previous 15 years. It reported on specificity, sensitivity, PPV, and negative predictive value (NPV). For LDCT, all noncalcified nodules with long axis diameter greater than or equal to 4 mm in the axial plane were considered as potentially positive for lung cancer. For CXR, all results were read from the original film or digital image and all noncalcified nodules and masses were considered as potentially positive for lung cancer.

Economic studies

Eight relevant economic studies[2,3,13-18] were identified of which one study was part of an HTA report.[3] Of the five studies from the USA, one study[13] was published in 2015, two studies[15,16] were published in 2014, one study[17] was published in 2013 and one study[18] was published in 2012. One study[3] was published from Canada in 2014, one study[14] was published from Japan in 2014 and one study[2] was published from Israel in 2013. Payer perspective was considered in three studies,[3,13,17] health care system perspective was considered in three studies,[2,16,18] societal perspective was considered in one study,[15] and the perspective was unclear in one study.[14] Time horizons were lifetime in four studies,[2,14-16] 25 years in one study,[3] 15 years in one study,[17] five years in one study,[13] and one year in one study.[18] Discounting rate was 3% in five studies,[2,3,13,15,16] not reported in one study,[14] not used in one study,[17] and not applicable in one study.[18] Six studies[2,3,13,16-18] compared LDCT screening with no screening or usual care, one study[15] compared LDCT screening with chest radiography or no screening, and one study[14] compared LDCT screening with chest radiography. Two studies[13,18] were on budget impact and reported on expenditures. Five studies[2,3,14-16] conducted cost-effectiveness analyses and reported incremental cost-effectiveness ratio (ICER) values and one study[17] conducted a cost-utility analysis and reported on cost-utility ratios. Key assumptions and model parameters for the included economic analyses are provided in Appendix 4. Terminology used here is as used by the study authors.

Evidence-based guidelines

Five evidence-based guidelines[17,19,21,23,27] that had recommendations regarding screening with LDCT in high risk persons (smokers or ex-smokers) were included. One guideline[19] was published by the United States Preventive Service Task Force (USPSTF) in 2014, one guideline[20] was published by the American College of Chest Physicians (ACCP) in 2013, one guideline[21] was published by American Cancer society (ACS) in 2013, one guideline[23] was published by Cancer Care Ontario (CCO) in 2013, and one guideline[17] was published by the American Association for Thoracic Surgery (AATS) in 2012. Grading of recommendations was mentioned in the guidelines by USPSTF and ACCP, as described in Appendix 5.

Summary of Critical Appraisal

The strength and limitations of the included HTAs, SRs, RCTs, economic studies and evidence-based guidelines are summarized below and details are provided in Appendix 6

Health Technology Assessments

The systematic review and economic study included in the included HTA[3] were critically appraised separately and are respectively included in the systematic review and economic study sections below.

Systematic review

All four systematic reviews,[3,5,6,11] including the systematic review in the HTA,[3] clearly stated the objective, provided the inclusion and exclusion criteria, searched multiple databases, described the individual study characteristics and declared conflicts of interest. In two systematic reviews[3,11] article selection was done by a single reviewer, in one systematic review[6] article selection was done in duplicate, and in one systematic review[5] it was unclear if article selection

was done in duplicate. Data extraction was done in duplicate in two systematic reviews,[6,11] done by a single reviewer in one systematic,[3] and it was unclear if it was done in duplicate in one systematic review.[5] Quality assessment of the included studies was conducted in three systematic reviews[3,5,6] and it was unclear if it was conducted in one systematic review.[11] The authors of the HTA[3] assessed the quality of the included systematic reviews with the AMSTAR tool and two systematic reviews scored six and one systematic review scored seven on a scale of 11. In one systematic review,[5] the included RCTs were of moderate to high quality. In one systematic review,[6] two of the included RCTs were assessed to have low risk of bias and the remaining were of variable quality and lacked details to enable a complete assessment. One systematic review[5] provided summary estimates by pooling results; however, there was considerable heterogeneity among the studies and a random effects model was used but the appropriateness of pooling is unclear. Publication bias was explored in one systematic review[5] and there was potential for bias. Publication bias was not explored in one systematic review[3] and it was unclear whether it was explored, in two systematic reviews.[6,11]

Randomized controlled trial

The NLST[7,12] was included in the selected systematic reviews and was not appraised separately. The study was considered of good quality as appraised as an interventional study; randomization was adequate, allocation was concealed, and outcomes assessment was blinded.

Economic studies

In all the included economic studies[2,3,13-18] the objective was stated, and the strategies compared, the time horizon, and the sources of clinical and cost data were stated. Sources of clinical and cost data were from the literature, registries and databases. Relevant cost data were considered for the analyses. The perspective was stated in all but one study.[14] Discounting was considered in five studies,[2,3,13,15,16] not reported in one study,[14] not used in one study,[17] and not applicable in one study.[18] Sensitivity analyses were incorporated in all the studies. The conclusions stated appeared to be consistent with the results reported. It should be noted, however, that in the conduct of the analyses several assumptions were made and the results need to be interpreted in the light of these assumptions.

Evidence-based guidelines

All five guidelines[17,19-21,23] stated the scope and purpose. The guideline development groups were composed of individuals with expertise in relevant areas such as radiology, oncology, and public health. In four guidelines[19-21,23] systematic reviews were conducted to gather evidence. In one guideline[22] a literature review was undertaken but it was not specifically mentioned if it was a systematic review. Evidence from RCTs was mainly used, however some cohort studies were also considered. Conflicts of interest of the authors were stated and there appeared to be no major issues. Recommendations with grading were provided in two guidelines[19,20] and there was no grading in three guidelines.[17,21,23] In all of the guidelines, it was unclear if cost implications and organizational barriers were considered or if patient input had been sought.

Summary of Findings

The findings are summarized below and the details are provided in Appendices 7 and 8.

What is the diagnostic accuracy of low-dose computed tomography for lung cancer screening in high-risk populations?

Systematic Review

One systematic review,[5] showed that the false-positive rate was statistically significantly higher with LDCT screening compared with CXR screening (OR 41.77, 95% confidence interval [CI] 5.18 to 336.95).

One systematic review,[11] showed that the PPV was 4.4% considering RCT data and 2.4% considering observational study data.

Randomized Controlled Trial

One RCT,[12] showed that the sensitivity, specificity, PPV, and NPV of lung cancer screening with LDCT were 93.8%, 73.4%, 3.8%, and 99.9% respectively. The sensitivity, specificity, PPV, and NPV of lung cancer screening with CXR were 73.5%, 91.3%, 5.7%, and 99.8% respectively.

What is the clinical effectiveness and safety of low-dose computed tomography for lung cancer screening in high-risk populations?

Health Technology Assessment

One HTA report,[3] including a systematic review of three systematic reviews found that screening with LDCT reduced cancer-related mortality in individuals aged 55 to 74 with a smoking history of 30 pack-years who were current smokers or who had quit smoking no more than 15 years previously. However, uncertainty still remains regarding the extent of benefit considering the high rate of false positives, overdiagnosis, and long-term radiation exposure.

Systematic Review

One systematic review,[5] showed that there was a statistically significantly increased chance of detecting lung cancers with LDCT in comparison with CXR odds ratio (OR) 3.38 and 95% CI of 1.8 to 6.35. Also, the chance of detecting stage 1 non-small cell lung cancer (NSCLC) was statistically significantly higher with LDCT compared with CXR, OR (95% CI) was 4.12 (2.03 to 8.37). Cancer-related mortality was statistically significantly reduced with LDCT, OR (95% CI) was 0.84 (0.74 to 0.96).

One systematic review[11] included both RCTs and observational studies. It showed that the detection rate with LDCT (cancers detected/ participant) was 1.1% based on RCT data and 1.0% in observational studies. The recall rate with LDCT (positive result/ participant) was 24.4% considering RCT data and 42.4% in observational studies. In the RCTs, there was a cut-off size for positive nodules but in the observational studies there was no cut-off size for positive nodules and this difference likely accounts for the difference in recall rates.

One systematic review,[6] showed that there was a 20% reduction in lung cancer-related mortality with LDCT screening compared with CXR when considering results of the NLST over a median follow-up of 6.5 years. Approximately 20% of individuals were found to have positive results while approximately 1% had lung cancer. The nodule detection rate per round of screening with LDCT varied between 3% and 30% in eight RCTs and between 5% and 51% in 13 cohort studies. In most studies, > 90% of the detected nodules were benign. The authors mentioned that in most instances, a detected nodule triggered further imaging, however the reporting of management protocols were inconsistent.

What is the cost-effectiveness of low-dose computed tomography for lung cancer screening in high-risk populations?

A cost-effectiveness study[3] conducted in Canada and considering a payer perspective and a time horizon of 25 years showed that for screening with LDCT compared with no screening, the ICER (cost per quality-adjusted life-year [QALY] gained) was $92,025 or $67,396 in case of annual screening or biennial screening, respectively. Sensitivity analyses conducted by varying the phase-in period and participation rate showed no substantial change. In these analyses, ICER values for annual screening varied between $89,468 and $97,847and for biennial screening varied between $60,727 and $69,829.

A cost-effectiveness study by Black et al.[15] conducted in USA and considering a societal perspective and lifetime time horizon showed that for screening with LDCT compared with no screening, the ICER was US$81,000 and the 95% CI was $52,000 to $186,000.

A cost-utility study by Villanti et al.[17] conducted in USA and considering payer perspective and a time horizon of 15 years, showed that for screening with LDCT compared with no screening the cost-utility ratio was US$28,240 per QALY gained.

A cost-effectiveness study by Wattson et al.[16] conducted in USA was on Hodgkin's lymphoma (HL) survivors. HL survivors are generally at risk of lung cancer due to the radiation treatment they had received. Considering health care system perspective and a lifetime time horizon, the study showed that for HL survivors who had been diagnosed with HL at 25 years and who were smokers and male, the ICER (cost/QALY) for screening with LDCT compared with no screening, varied between US$34,841 and US$78, 890 depending on the prior radiation treatment received for HL. Screening with LDCT appears to be more cost-effective for smokers rather than non-smokers. ICERs for other subgroups of HL survivors varied between US$11,252 and US$795,685 and are available in Appendix 7.

A cost-effectiveness study by Shmueli et al.[2] conducted in Israel and considering a health care system perspective and a lifetime time horizon showed that for screening with LDCT compared with usual care, the ICER was US$1464.The incremental cost for LDCT compared to usual care was low (US$ 86.47) and the QALY gained was 0.059, accounting for the low ICER value.

A cost-effectiveness study by Tabata et al.[14] conducted in Japan and considering a lifetime time horizon showed that for screening with LDCT compared with chest radiography, in the case of males, the ICER (Japanese Yen/life-year gained) values were 1,400,000 for age 55 to 59 years, 678,000 for 60 to 64 years, 550,000 for 65 to 69 years and 268,000 for 70 to 74 years. The perspective considered for the analysis was not described. ICERs for other subgroups are available in Appendix 7

One fiscal impact study by Roth et al.[13] conducted in USA showed that over five years the expenditure would be US$ 24 billion for screening with LDCT and US$ 17.2 billion in case of no screening.

One budget impact study by Goulart et al.[18] showed that LDCT screening for lung cancer would increase national annual healthcare expenditures by US$1.3 to US$2.0 billion, depending on adherence.

What are the evidence-based guidelines regarding the use of low-dose computed tomography for lung cancer screening

All five guidelines[17,19-21,23] recommended, annual LDCT screening for people with a smoking history of at least 30 pack-years and who currently smoke or have quit within the last 15 years. The recommended age range was 55 to 80 years in the USPSTF guideline,[19] 55 to 79 years in the AATS guideline[17] and 55 to 74 in the ACCP, ACS, and CCO guidelines.[20,21,23] In addition, the ACS guideline[21] recommended annual LDCT screening until the age of 79 years for long-term lung cancer survivors, in order to detect second primary lung cancers. The USPSTF guideline[19] also recommended that LDCT screening should be discontinued if a person has not smoked for 15 years or has developed a health problem which significantly limits life expectancy or the ability or willingness to have curative lung surgery. More details are provided in Appendix 8.

Limitations

There was considerable overlap in the studies included in the systematic reviews. Hence results may not be mutually exclusive. However, this limitation is somewhat mitigated by the fact that not all the same outcomes were reported in the systematic reviews.

Information on follow-up procedures and subsequent treatment in the case of a positive screen result was lacking.

Sensitivity and specificity values were obtained from a single study. However the estimates were based on a large study population (N = 53,454). Details as to how sensitivity and specificity were determined were lacking.

In the economic studies, comparison between studies was difficult as assumptions and model parameters varied.

Overdiagnosis estimates may not be accurate as there appears to be no standard method for determining overdiagnosis. Overdiagnosis refers to lung cancers that were identified by screening and would not affect the person if left untreated.

The recommendations in the evidence-based guidelines were not always graded, hence the level of evidence and strength of the recommendation was unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One HTA report, three systematic reviews, one RCT, seven economic studies and five evidence-based guidelines were included in this review.

The sensitivity and specificity with LDCT were respectively 93.8% and 73.4%. The PPV ranged between 2.4% to 4.4%. The NPV was 99.9%.

Screening for lung cancer with LDCT resulted in detection of early-stage cancers and reduced cancer-related mortality. However, the high rate of false positives, can lead to unnecessary work-up of benign nodules.

The ICER (cost/QALY) for screening with LDCT varied between US$11,252 and US$795,685 across the North American studies depending on the scenario. These extreme values were for HL survivors; US$ 11,252 for male smokers with HL diagnosed at age 35 years and treated with mantle (30 Gy) and US$795,685 for male non-smokers with HL diagnosed at age 35 years and treated with involved field radiation therapy (20 Gy). A Canadian cost-effectiveness study reported ICERs (CAN$/QALY gained) of 92,025 and 67,390 for annual screening and for biennial screening, respectively.

The evidence-based guidelines recommended annual lung cancer screening with LDCT for people with a smoking history of at least 30 pack-years and who currently smoke or have quit within the last 15 years.

The benefit from reduced mortality with lung cancer screening with LDCT needs to be weighed against the harms incurred due to high rate of false-positive screen results and overdiagnosis. More information will likely be available when the comprehensive review on lung cancer screening from the Canadian Task Force on Preventive Health Care is published; presently the protocol[28] is available. There are a number of ongoing trials,[3] results of which may provide further insights regarding lung cancer screening with LDCT.

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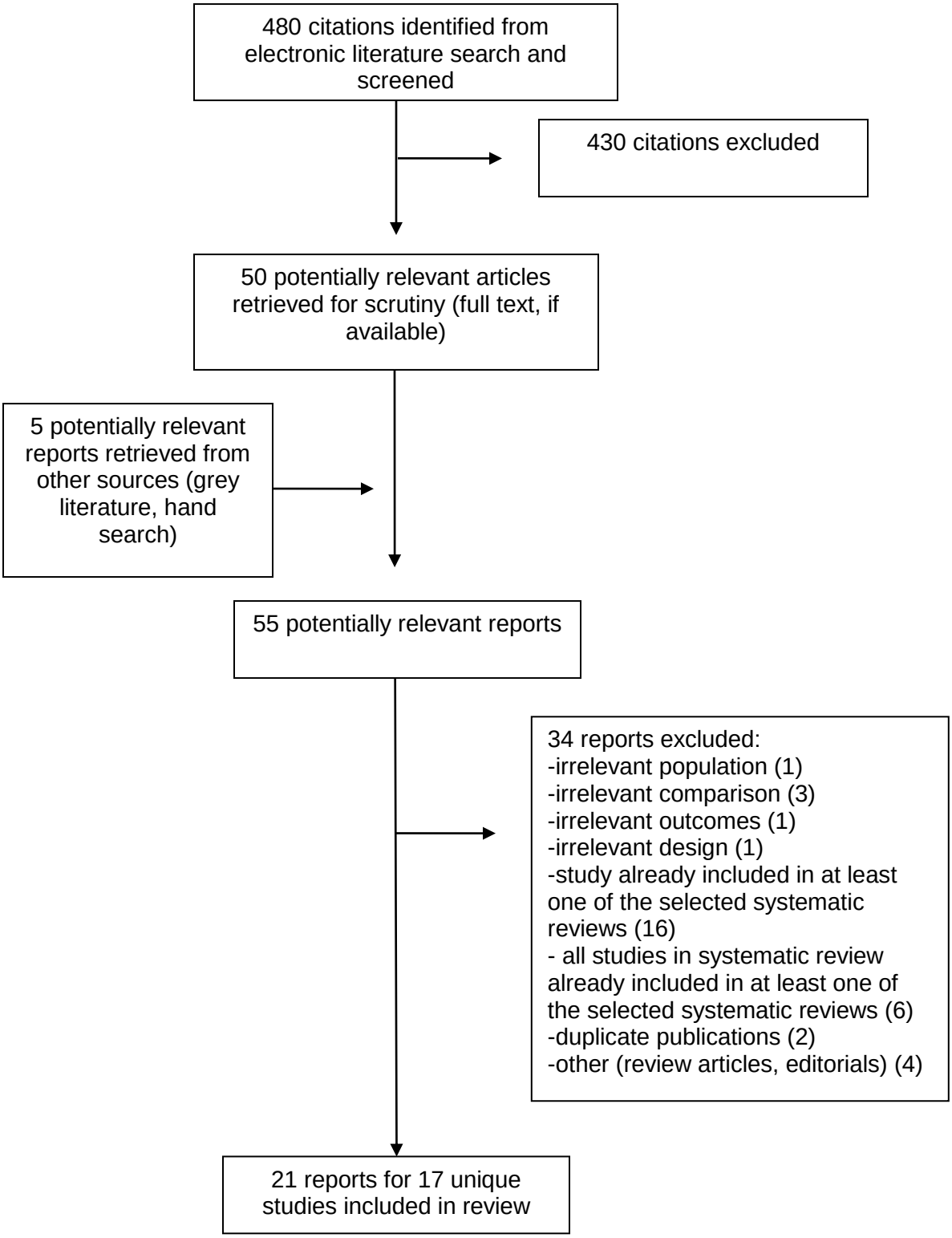
ABBREVIATIONS

AATS	American Association for Thoracic Surgery
ACCP	American College of Chest Physicians
ACS	American Cancer Society
CCO	Cancer care Ontario
CI	confidence interval
CMS	Centers for Medicare and Medicaid Services
CR	conventional radiography
CXR	chest x-ray
DANTE	Detection and Screening of Early Lung Cancer by Novel Imaging Technology
DLST	Danish lung cancer screening trial
Gy	Gray
HL	Hodgkin's lymphoma
ICER	incremental cost-effectiveness ratio
IFRT	involved-field radiation therapy
LDCT	low-dose computed tomography
NLST	National Lung Cancer Screening Trial
OR	odds ratio
PPV	positive predictive value
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SEER	Surveillance, Epidemiology and End Results
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task force
WTP	willingness to pay
WTPT	willingness to pay threshold

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (N)	Comparison	Outcomes Measured
Health Technology Assessment				
Alberta STE report,[3] 2014, Canada	HTA which comprised of a systematic review of three systematic reviews, a cost-effectiveness analysis and a budget impact analysis. Economic section: Cost-utility analysis was undertaken. Perspective: Canadian payer, Time horizon: 25 years, Discounting: 3%	Asymptomatic adults (aged ≥50 years) with a history of smoking Persons at risk of lung cancer	LDCT versus no screening or usual care	Clinical: Mortality Economic: ICER, Budget impact analysis
Systematic Review				
Fu,[5] 2014, China	Systematic review included 9 RCTs	Smokers/ex-smokers in the age range 50 to 80 years N varied between 190 to 4104	LDCT versus CXR or no screening	Mortality, lung cancer detection, false-positive rate
Seigneurin,[11] 2014, UK	Systematic review included 16 studies (10 RCTs and six observational studies)	Smokers and ex-smokers in the age range 50 to 75 years in the RCTs, Smokers and ex-smokers of age >40 years in the observational studies	LDCT versus CXR or no screening	Recall rates, detection rates, PPV
Bach,[6] 2012, USA	Systematic review included 21 studies (8 RCTs and 13 observational studies)	For RCTs N varied between 190 and 53,454 and the age ranges varied between 47 and 80 years. For observational studies N varied between 60 and 5,201 and the age ranges varied between 40 and 80 years	LDCT versus CXR or no screening	Mortality, nodule detection

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (N)	Comparison	Outcomes Measured
Randomized Controlled Trial				
NLST,[7,12] 2013 and 2011, USA	Randomized	Persons at high risk of lung cancer. Age range 55 to 74 years N = 53,454	LDCT versus CXR	Sensitivity, specificity, positive screens

CXR = chest X-ray, HTA = health technology assessment, ICER = incremental cost-effectiveness ratio, LDCT – low-dose computed tomography, NLST = National Lung Cancer Screening Trial, RCT = randomized controlled trial

APPENDIX 3: Characteristics of economic studies

Author, Year, Country	Study design[a]	Perspective, Time horizon, Currency, Discounting	Population	Interventions	Outcomes[a]
Roth,[13] 2015, USA	Simulation model to forecast impact of the of the Centers for Medicare and Medicaid Services (CMS) LDCT screening policy compared with no screening	Perspective: Medicare payer Time horizon: 5 years Currency: US$ Discounting: 3% per year	Medicare enrollee age 55 to 77 years eligible for LDCT screening	Screening with LDCT versus no screening	Total and per enrollee per month fiscal impact
Black,[15] 2014, USA	Cost-effectiveness analysis Objective: To examine the cost-effectiveness of screening with LDCT in the NSLT	Societal perspective. Within-trial time horizon and lifetime time horizon Currency: US $ Annual discounting rate of 3%	High-risk population (patients of the rct: NLST)	LDCT, radiography or no screening	ICER
Tabata,[14] 2014, Japan	Cost-effectiveness analysis Iinuma's mathematical model was used Objective: To examine the	Perspective: NR Time horizon: Lifetime Currency: Japanese Yen Discounting rate: NR	Japanese smokers of age 55 to 74 years	LDCT versus chest radiography	ICER

Author, Year, Country	Study design[a]	Perspective, Time horizon, Currency, Discounting	Population	Interventions	Outcomes[a]
	appropriate age and costs of LDCT lung cancer screening in Japanese smokers of age 55 to 74 in terms of cost-effectiveness				
Wattson,[16] 2014, USA	Cost-effectiveness analysis Markov model used Objective: To develop a decision analytic and cost-effectiveness model to estimate the benefits and harms of annual LDCT screening among HL survivors	Perspective: Health care system Time horizon: Lifetime Currency: US $ (2013) Discounting rate of 3%	Hodgkin lymphoma survivors (generally at risk of secondary lung cancer)	LDCT versus no screening	ICER
Shmueli,[2] 2013, Israel	Cost-effectiveness analysis A decision analytic framework was used Objective: To determine	Perspective: Health care system Time horizon: Lifetime Currency: US$ (2011)	Moderate to heavy smokers of age 45 years or older (N =842)	LDCT versus usual care	ICER

Author, Year, Country	Study design[a]	Perspective, Time horizon, Currency, Discounting	Population	Interventions	Outcomes[a]
	the cost-effectiveness of lung cancer screening versus usual care in Israel	Discounting rate of 3%			
Villanti,[17] 2013, USA	Cost-utility analysis Objective: To determine cost-effectiveness of LDCT screening for lung cancer in a hypothetical cohort of adults aged 50 to 64 years, at high risk of lung cancer and to quantify the additional benefit resulting from addition of smoking cessation program to the screening program	Perspective: Commercial payer Time horizon: 15 years Currency: US$ (2012) Discounting not used.	Adults of age 45 to 64 years at high risk of lung cancer (hypothetical cohort)	Screening with LDCT versus no screening	Cost-utility ratio
Goulart,[18] 2012, USA	Budget impact model Objective: To estimate the additional expenditures that would be incurred if LDCT	Perspective: Healthcare payer and patient perspective Time horizon: 1 year	Persons eligible for lung cancer screening (based on the criteria in NLST)	LDCT versus no screening	Expenditure

Author, Year, Country	Study design[a]	Perspective, Time horizon, Currency, Discounting	Population	Interventions	Outcomes[a]
	screening is widely accepted in the United States	Currency: US$ (2011) Discounting: NA			

CMS = Centers for Medicare and Medicaid Services, ICER = incremental cost-effectiveness ratio, LDCT = low-dose computed tomography, NLST = National lung cancer screening trial, NA = not applicable, NR = not reported, US = United States

[a]Study design terminology is as mentioned by the study authors

APPENDIX 4: Main assumptions and parameters used in the economic analysis

Author, Year, Country	Study assumptions and parameter
Roth,[13] 2015, USA	Only high-risk Medicare enrollees were considered. It was assumed that 30% of high-risk enrollees were offered LDCT screening in 2015 and an additional 15% for each subsequent year up to 2019. Among those offered screening only a certain proportion was assumed to proceed to screening (50% in year 1 to 70% in year 5), based on historical patient behaviour with analogous screening technologies. In the no screen scenario, similar calculations as for LDCT screening group were done but the lung cancer was clinically detected. In accordance with CMS policy, it was assumed there were no copayments or coinsurance to offset the Medicare program expenditures. Lung cancer mortality rates were from the SEER database.
Black,[15] 2014, USA	Several assumptions were made in the base case analysis to reduce the complexity and minimize use of variables for which reliable estimates were not available. Assumptions for the base case, included: zero number of future excess cases, intermediate survival for stage 1A NSCLC, cost of LDCT screen was $285, one follow-up LDCT screening, cost of surgery was US$22,000, 1.2% surgical mortality, no future health care costs after LDCT screening or no screening, reduction in QoL after a positive screen was zero and after diagnosis of stage 1a NSCLC was 0.03, cost of managing potentially significant incidental finding was US$500, and radiation induced lung cancer deaths per lung cancer death prevented was 0.046.
Tabata,[14] 2014, Japan	Results were presented for by gender (male and female) and by age groups (55 to 59 years, 60 to 64 years, 65 to 69 years and 70 to 74 years), i.e. eight separate groups. In the reference case RR for lung cancer among smokers was 4.39 for males and 2.79 for females, mortality was 30% for early cancer and 85% for advanced cancer, early lung cancer and advanced lung cancer detected were respectively 50% and 50% with CR and 85% and 15% with LDCT, rate of requiring thorough screening was 7% for CR and 20% for LDCT, cost of screening was 1,500 yen with CR and 10,000 yen with LDCT, overdiagnosis was 0% for CR and 10% for LDCT, cost of treatment in 10,000 yen was 150 and for early cancer and 300 for advanced cancer, and screening interval was 1 year. Overdiagnosis/ positive self selection was assumed to be 10%.
Wattson,[16] 2014, USA	Assumptions and parameters for base case. RR for lung cancer in HL survivors who were treated at age 25, 35 and 60 years were 7.96, 4.82 and 2.02 respectively. Stage distribution of NSCLC in screened population was localized (57.1%), regional (21.2%) and distant (21.7) and in unscreened population was localized (20.3%), regional (28.9%) and distant (50.8%). Probability of false-positive with LDCT was 28.2% for years 1 to 5 and 16.7% for years 6 and later. Lead time bias in years was assumed to be zero. Overdiagnosis and length time was assumed to be zero. Cost of diagnostic tests as part of false-positive work varied between US$ 223 and US$1246 depending on what was entailed. Cost of LDCT screen was assumed to be US$223.
Shmueli,[2] 2013, Israel	Some assumptions and parameters of the base case are described here. The cost of screening, including the LDCT and any further diagnostic and curative treatments as a result of screening findings were calculated using actual unit cost of service at the authors' institution. For Stage 1 patients with disease progression, it was assumed recurrence occurred 2 years after diagnosis and progressed to stage IV. Diagnosed

Author, Year, Country	Study assumptions and parameter
	population was 75% male and 25% female. Cure rate was 70% for stage I diagnosis. LDCT cost was $74. Probabilities of stage1 were 0.833 in LDCT screening and 0.115 in usual care. Probabilities of stage II and III were 0.083 in LDCT screening and 0.191 in usual care. Probability of positive results was 0.109 and probability of true positive was 0.130.
Villanti,[17] 2013, USA	For base case, probabilities of lung cancer stage A, stage B and stage C were respectively 17.4%, 14.6% and 68.0% for the unscreened population and 79.3%, 16.2% and 4.5% in the screened population. The A, B, and C stages correspond approximately to Surveillance, Epidemiology and End Results (SEER) program's localized, regional, and distant categories. Negative results (no nodules present or semi-positive) were assumed to be 79% and positive results (nodule > 5 mm) were assumed to be 21 %. Utility weights for patients with stage A, B and C were respectively 0.823, 0.772, and 0.573. LDCT screen cost was US$ 210. Lead time for all screen detected cancer was 2 years.
Goulart,[18] 2012, USA	Screening uptake rates were based on current screening rates reported for breast cancer (75%) and colorectal cancer (50%). The annual number of persons with positive LDCT screening results was assumed to be 28% based on data from NLST. The false-positive rate was assumed to be 96.4% Screening detected cases according to cancer stage were 57.1% for localized, 21.2% for regional and 21.7% for distant. For the no screening scenario, cancer detected cases according to cancer stage were 16.1% for localized, 23.7% for regional and 60.2% for distant. To estimate expenditure related to LDCT screening, Centres for Medicare and Medicaid service Health care Common Procedure Coding system and Diagnostic related group codes and relevant Medicare fees were used.

CMS = Centers for Medicare and Medicaid Services, CR = conventional radiography, LDCT = low-dose computed tomography, NSCLC = non-small cell lung cancer, QoL = quality of life, RR = relative risk, SEER = Surveillance, Epidemiology and End Results

APPENDIX 5: Grading of Recommendations and Levels of Evidence

<table>
<tr><th>Guideline Society and/or Author, Year, Country, Topic</th><th>Recommendation Grade and Level of Evidence</th></tr>
<tr><td>USPSTF,[19] 2014 USA</td><td>
<table>
<tr><th>Grade</th><th>Definition</th><th>Suggestions for Practice</th></tr>
<tr><td>A</td><td>“The USPSTF recommends the service. There is high certainty that the net benefit is substantia”
Page 339</td><td>“Offer/provide this service”
Page 339</td></tr>
<tr><td>B</td><td>“The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.”
Page 339</td><td>“Offer/provide this service”
Page 339</td></tr>
<tr><td>C</td><td>“The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.”
Page 339</td><td>“Offer/provide this service for selected patients depending on individual circumstances.”
Page 339</td></tr>
<tr><td>D</td><td>“The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.”
Page 339</td><td>“Discourage the use of this service”
Page 339</td></tr>
</table>
</td></tr>
<tr><td>ACCP,[20] 2013, USA; Summary[26]</td><td>
<table>
<tr><th>Grade of Recommendation</th><th>Benefit vs. Risk and Burdens</th><th>Methodologic Quality of Supporting Evidence</th><th>Implications</th></tr>
<tr><td>1A
“Strong recommendation, high-quality evidence”
Page 4 of 9</td><td>“Benefits clearly outweigh risk and burdens or vice versa”
Page 4 of 9</td><td>“Consistent evidence from randomized controlled trials (RCTs) without important limitations or</td><td>“Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change</td></tr>
</table>
</td></tr>
</table>

Guideline Society and/or Author, Year, Country, Topic	Recommendation Grade and Level of Evidence			
			exceptionally strong evidence from observational studies" Page 4 of 9	confidence in the estimate of effect" Page 4 of 9
	1B "Strong recommendation, moderate-quality evidence" Page 4 of 9	"Benefits clearly outweigh risk and burdens or vice versa" Page 4 of 9	"Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies" Page 4 of 9	"Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate" Page 4 of 9
	1C Strong recommendation, low- or very-low quality evidence Page 4 of 9	"Benefits clearly outweigh risk and burdens or vice versa" Page 4 of 9	"Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence" Page 4 of 9	"Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate" Page 4 of 9
	2A "Weak recommendation, moderate-quality evidence" Page 4 of 9	"Benefits closely balanced with risks and burden" Page 4 of 9	"Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies" Page 4 of 9	"The best action may differ depending on circumstances or patient's or societal values. Further research is very unlikely to change confidence in the estimate of effect" Page 4 of 9

Guideline Society and/or Author, Year, Country, Topic	Recommendation Grade and Level of Evidence			
	2B "Weak recommendation, moderate-quality evidence" Page 4 of 9	"Benefits closely balanced with risks and burden" Page 4 of 9	"Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies" Page 4 of 9	"Best action may differ depending on circumstances or patient's or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate" Page 4 of 9
	2C "Weak recommendation, low- or very-low quality evidence" Page 4 of 9	"Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced" Page 4 of 9	"Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect Evidence" Page 4 of 9	"Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate" Page 4 of 9
ACS,[21] USA, 2013	No grading used			
Cancer Care Ontario,[23] Canada, 2013	No grading used			
AATS,[22] 2012, USA	No grading used			

APPENDIX 6: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Health Technology Assessment		
Alberta STE report,[3] 2014, Canada (Quality assessment of clinical section of the HTA report)	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, Jan 2011 to Dec 2013. Relevant websites and reference list of relevant articles were searched. • Study selection was described and flow chart was presented. • List of included and excluded studies was provided. • Characteristics of the individual studies (systematic reviews) were provided. • Quality assessment of the systematic reviews were conducted using AMSTAR. • Conflicts of interest of the authors were stated.	• Article selection, data extraction and quality assessment was done by a single reviewer – a potential limitation. • The included systematic reviews did not explore publication bias. • A narrative summary of the findings was presented.
Systematic review		
Fu,[5] 2014, China	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, January 1994 to September 2013 and relevant websites. • Study selection was described and flow chart was presented. • List of included studies was provided. • Characteristics of the individual studies were provided. • Quality assessments of studies were conducted and they were of reasonable quality. • Results were pooled to provide summary estimates, however there was considerable heterogeneity among studies and a random effects model was used to compensate for this.	• List of excluded studies was not provided • Unclear if article selection and data extraction were done in duplicate. However, quality assessment was done by two reviewers

First Author, Publication Year, Country	Strengths	Limitations
	• Publication bias was explored using Funnel plots and there was potential for bias. • The authors stated that there was no conflict of interest.	
Seigneurin,[11] 2014, UK	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, January1980 to June 2013. • Study selection was described and flow chart was presented. • List of included studies was provided. • Data extraction was done in duplicate. • Characteristics of the individual studies were provided. • Meta-regression was conducted. • The authors stated there was no conflict of interest.	• List of excluded studies was not provided • Article selection was done by a single reviewer • Unclear if quality assessment of the studies was undertaken • Unclear if publication bias was explored
Bach,[6] 2012, USA	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, 1996 to April 2012. • List of included studies was provided. • Characteristics of the individual studies were provided. • Article selection and data extraction were done in duplicate. • Quality assessments of the studies were conducted. • Conflict of interest was stated and there appeared to be no issues.	• Study selection was not described and flow chart was not presented • List of excluded studies was not provided • Publication bias was not explored
RCT		
NLST,[7,12] 2013 and 2011, USA	Though the NLST is included in the selected systematic reviews, these two publications of NLST included here are for the outcomes (such as sensitivity and specificity) which were not discussed in the included systematic reviews and which are relevant for addressing the question on diagnostic accuracy. These two publications do not contain the information required to assess the quality of the trial. However other systematic reviews have assessed the quality of the NLST and it was found to be of good quality.[5,6] Hence, further quality assessment was not undertaken.	

First Author, Publication Year, Country	Strengths	Limitations
Economic studies		
Roth,[13] 2015, USA	• Objectives were stated. • The strategies compared were stated. • Time horizon and perspective were stated. • Clinical data were obtained from several sources such as the NLST data, SEER database and literature. • Cost data source were stated. • Extent of discounting was stated (3%). • Simulation model was used. • Sensitivity analyses were conducted. • Conclusions appear to be consistent with the results reported.	• Estimates were calculated based on several assumptions.
Alberta STE report,[3] 2014, Canada (Quality assessment of economic section of the HTA report)	• Objectives were stated. • The strategies compared were stated. • Time horizon and perspective were stated. • Clinical data were obtained from several sources such as the NLST data, SEER database and literature. • Cost data source were stated. • Extent of discounting was stated (3%). • Cost-utility analysis. • Sensitivity analyses were conducted. • Conclusions appear to be consistent with the results reported.	• Estimates were calculated based on several assumptions
Black,[15] 2014, USA	• Objectives were stated. • The strategies compared were stated. • Time horizon and perspective were stated. • Clinical data were obtained from the literature. • Cost data source were stated. • Extent of discounting was stated (3%).	• Estimates were calculated based on several assumptions.

First Author, Publication Year, Country	Strengths	Limitations
	• Markov state transition model was used. • Incremental analysis was reported. • Sensitivity analyses were conducted. • Conclusions appear to be consistent with the results reported.	
Tabata,[14] 2014, Japan	• Objectives were stated. • The strategies compared were stated. • Time horizon was stated. • Clinical data were obtained from the literature and regional cancer registries. • Cost data source were from literature and registries. • Iinuma's mathematical model was used. • Incremental analysis was reported. • Sensitivity analyses were conducted. • Conclusions appear to be consistent with the results reported.	• Estimates were calculated based on several assumptions. • Discounting rate not mentioned. • Indirect costs were not considered. • Some discrepancies in reporting of the results in the text and figures.
Wattson,[16] 2014, USA	• Objectives were stated. • The strategies compared were stated. • Time horizon and perspective were stated. • Clinical data were obtained from population databases, HL-specific literature and NLST. • Cost data source were stated (such as CMS/Medicare fee schedule, Consumer price index. • Extent of discounting was stated (3%). • Incremental analysis was reported. • Sensitivity analyses were conducted. • Conclusions were consistent with the results reported.	• Estimates were calculated based on several assumptions.

First Author, Publication Year, Country	Strengths	Limitations
Shmueli,[2] 2013, Israel	• Objectives were stated. • The strategies compared were stated. • Time horizon and perspective were stated. • Clinical data source were stated (such as database, registry). • Cost data source were stated (such actual costs at the authors institution). • Extent of discounting was stated (3%). • Incremental analysis was reported. • Sensitivity analyses were conducted. • Conclusions were consistent with the results reported.	• Estimates were calculated based on several assumptions.
Villanti,[17] 2013, USA	• Objectives were stated. • The strategies compared were stated. • Time horizon and perspective were stated. • Clinical data sources were stated (such as literature). • Cost data source were stated (such as commercial claims database). • Cost-utility analysis was reported. • Sensitivity analyses were conducted. • Conclusions were consistent with the results reported.	• Discounting was not used. However, the authors stated that as medical cost inflation had exceeded discount rates during the past 15 years, their 2012 cumulative tabulation of costs would have produced lesser costs if prior years cost were multiplied by discount rates to bring costs to 2012 level. • Estimates were calculated based on several assumptions.
Goulart,[18] 2012, USA	• Objectives were stated. • The strategies compared were stated. • Time horizon and perspective were stated. • Clinical data source were stated (such as data from NLST, andCDC National Health Interview Survey [NHIS]). • Cost data source were stated (such as commercial claims database, and Medicare). • Discounting not applicable as a 1-year study.	• Estimates were calculated based on several assumptions. • Indirect costs were not considered.

First Author, Publication Year, Country	Strengths	Limitations
	• Budget impact analysis was reported. • Sensitivity analyses were conducted. • Conclusions were consistent with the results reported.	
Guidelines		
USPSTF,[19,25] USA, 2014	• The scope and purpose were clearly stated. • The guideline development group comprised of individuals from relevant areas (such as clinical, public health). • The methods used for the development of the guidelines appear to be rigorous (multiple database searched, systematic review conducted with article selection done by two reviewers, data extraction done by one reviewer and checked by another reviewer). • Internal and external reviews of the guidelines were conducted. • Recommendations were graded. • Conflicts of interest of guideline development group members were stated.	• Cost implications or organizational barriers were not discussed. • Unclear if patient input was sought.
ACCP,[20] 2013, USA,	• The scope and purpose were clearly stated. • The guideline development group comprised of individuals with relevant expertise. • The methods used for the development of the guidelines appear to be rigorous. The systematic review on which the guideline was based was well conducted. Article selection and data extraction were done in duplicate. • Internal and external review. • Recommendations were graded. • Conflicts of interest of guideline development group members were stated.	• Cost implications or organizational barriers were not discussed. • Unclear if patient input was sought.
ACS,[21] USA, 2013	• The scope and purpose were clearly stated.	• Recommendations were not graded.

First Author, Publication Year, Country	Strengths	Limitations
	• The guideline development group comprised of individuals from relevant areas (such as clinical, biostatistics, public health). • The methods used for the development of the guidelines appear to be rigorous. Systematic review conducted, but the number of databases searched were not specified. • Externally reviewed (journal publication). • Conflicts of interest of guideline development group members were stated.	• Cost implications or organizational barriers were not discussed. • Unclear if patient input was sought.
Cancer Care Ontario,[23] Canada, 2013	• The scope and purpose were clearly stated. • The guideline development group comprised of individuals from relevant areas (such as medical imaging, radiation oncology, respirology, prevention and cancer control). • The methods used for the development of the guidelines appear to be rigorous (multiple database searched, systematic review conducted). • Internal and external reviews of the guidelines were conducted. • Conflicts of interest of guideline development group members were stated.	• Recommendations were not graded. • Cost implications or organizational barriers were not discussed. • Unclear if patient input was sought.
AATS,[22] 2012, USA	• The scope and purpose were clearly stated. • The guideline development group comprised of individuals from relevant areas (such as thoracic surgery, oncology, pulmonology, radiology). • Evidence appears to have been obtained from literature review. • External review of the guidelines were conducted (journal publication). • Conflict of interest of guideline development group members were stated.	• Unclear if internal review was conducted. • Recommendations were not graded. • Cost implications or organizational barriers were not discussed. • Unclear if patient input was sought.

APPENDIX 7: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Health Technology Assessment</td></tr>
<tr><td>Alberta STE report,[3] 2014, Canada</td><td>Main Findings:
Clinical
<table>
<tr><th>Included systematic review</th><th>No. and design of included studies and comparisons</th><th>Reviewer's comment</th></tr>
<tr><td>Bach, 2012</td><td>RCT: 8
3 LDCT vs. CXR
5 LDCT vs. no screening
Cohort studies: 13 LDCT</td><td>"Screening a population of individuals at a substantially elevated risk of lung cancer most likely could be performed in a manner such that the benefits that accrue to a few individuals outweigh the harms that many will experience. However, substantial uncertainties exist regarding how to translate that conclusion into clinical practice." Page 84</td></tr>
<tr><td>Humphrey, 2013</td><td>RCT: 7[a]
1 LDCT vs. CXR
3 LDCT vs. no screening
Cohort studies: 13 LDCT

([a]Review of effectiveness of LDCT was limited to 4 RCTs)</td><td>"LDCT screening seemed to reduce lung cancer mortality. This result was driven by one large, good-quality study conducted in the US. Given the high number of current and former smokers in the population at risk for lung cancer, identifying and treating early-stage lung cancer with screening will hopefully clarify the balance of benefits and harms associated with screening. In addition, more work in public health to reduce smoking remains the most important approach to reducing morbidity and mortality from lung cancer." Page 84</td></tr>
<tr><td>Manser, 2013</td><td>RCT: 9
8 CXR/sputum vs. no screening
1 LDCT vs. CXR</td><td>"Annual low-dose CT screening is associated with a reduction in lung cancer mortality in high-risk smokers but further data are required on the cost effectiveness of screening and the relative harms and benefits of screening across a range of different risk groups and settings. More data are needed on the cost effectiveness of screening that take into account the frequency of screening and both the benefits and harms, before recommendations can be made for large-scale screening programs." Page 84</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
Economic
Cost-effectiveness analyses
<table>
<tr><th>Scenario</th><th>Costs ($)</th><th>Incremental costs ($)</th><th>QALY</th><th>Incremental QALY</th><th>ICER ($ per QALY gained)</th></tr>
<tr><td>Annual screening</td><td>1,599,277,626</td><td>422,347,222</td><td>63,908,438</td><td>4,589</td><td>92,025</td></tr>
<tr><td>Biennial screening</td><td>1,418,470,164</td><td>241,539,760</td><td>63,907,433</td><td>3,584</td><td>67,396</td></tr>
<tr><td>No screening</td><td>1,176,930,404</td><td>-</td><td>63,903,849</td><td>-</td><td>-</td></tr>
<tr><td colspan="6">Based on assumptions of a 25-year time period, a 70% participation rate, a five-year phase-in period, and a 3% risk of lung cancer</td></tr>
</table>
Sensitivity analyses conducted by varying phase-in period and participation rate showed no substantial change. ICER ($ per QALY gained) for annual screening varied between 89,468 to 97,847 and for biennial screening varied between 60,727 and 69,829.

Budget impact analysis
"For annual screening, the budget impact in 2012 is $11.56 million, with costs increasing to $32.88 million in 2016. After 2016, the budget impact is more stable, at approximately $30 million per year. The cumulative costs over the 20-year span are approximately $542 million. A similar pattern is observed for biannual screening where the cost impact increases between 2012 and 2015, and remains steady after 2015. The cumulative cost over the 20-year span for biennial screening is $309 million." Page 92
</td></tr>
<tr><td></td><td>
Authors' Conclusion:
"Three good quality systematic reviews and two Canadian literature reviews that have examined the existing scientific evidence on the potential benefits and harms of LDCT for lung cancer screening unanimously conclude that the results of the NLST trial provide definitive evidence that LDCT screening can reduce lung cancer-related and all-cause mortality in individuals aged 55 to 74 with a smoking history of 30 pack-years who are current smokers or who quit smoking no more than 15 years previously. There remains great uncertainty about the degree of benefit of screening in settings that depart from that of the NLST, either in setting or with regard to individuals being screened, as well as the potential harms that may be caused due to false positive results, overdiagnosis, and long-term radiation exposure. The results of trials currently ongoing should help to reduce some of this uncertainty." Page 69

"Assuming that the efficacy estimates from the NLST trial hold, screening for lung cancer with LDCT is associated with both additional costs and health benefits. In a constrained health care system, other services will need to be contracted or eliminated to free the approximately $105.68 million (for annual screening) in resources that is needed to fund its adoption for the first five years alone. Determining whether the $105.68 million is worth the investment depends on the opportunity cost of its adoption. That is, if decision-makers were to adopt lung cancer screening with LDCT,
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>it is imperative that they consider carefully what services would be contracted or eliminated in order to fund its adoption, and must assess the associated costs and health impacts compared to lung cancer screening with LDCT. For annual screening, the opportunity cost would have to be higher than $92,025 per additional QALY gained ($67,396 for biennial screening) in order for lung cancer screening with LDCT to be considered cost effective." Page 97</td></tr>
<tr><td colspan="2">Systematic review</td></tr>
<tr><td>Fu,[5] 2014, China</td><td>Main Findings:
Results with LDCT versus CXR or no screening
<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>OR (95% CI)</th><th>Heterogeneity I^2</th></tr>
<tr><td>Stage I NSCLC detected</td><td>9</td><td>4.12 (2.03 to 8.37)</td><td>64%</td></tr>
<tr><td>Total lung cancers detected</td><td>9</td><td>3.38 (1.8 to 6.35)</td><td>83%</td></tr>
<tr><td>Lung cancer-specific mortality</td><td>4</td><td>0.84 (0.74 to 0.96)</td><td>48%</td></tr>
<tr><td>All-cause mortality</td><td>4</td><td>1.18 (0.86 to 1.63)</td><td>73%</td></tr>
<tr><td>False-positive rate</td><td>5</td><td>41.77 (5.18 to 336.95)</td><td>98%</td></tr>
</table>
Authors' Conclusion:
"Among the risky population, LDCT screening find out more stage I lung cancers and total lung cancers compared with chest X-ray or no screening, and also shows advantages in decreasing lung cancer-specific mortality, but the screening method does not decrease all-cause mortality and have a higher false-positive rates in diagnosis." Page 1 of 9</td></tr>
<tr><td>Seigneurin,[11] 2014, UK</td><td>Main Findings:
Recall rates, detection rates and PPV at prevalent screen with LDCT
<table>
<tr><th>Category</th><th>Recall rate % (positive result/ participant)</th><th>Detection rate % (cancers detected/ participants)</th><th>PPV % (cancers detected/ positive results)</th></tr>
<tr><td colspan="4">Study type</td></tr>
<tr><td>Observational</td><td>42.4 (7819/18 428)</td><td>1.0 (185/18 428)</td><td>2.4 (185/7819)</td></tr>
<tr><td>RCT</td><td>24.4 (10 947/44 944)</td><td>1.1 (484/44 944)</td><td>4.4 (484/10 947)</td></tr>
<tr><td colspan="4">Cut-off size for solid non-calcified nodules</td></tr>
<tr><td>None</td><td>40.7 (8200/20 132)</td><td>1.1 (223/20 132)</td><td>2.7 (223/8200)</td></tr>
<tr><td>3 - 4</td><td>25.0 (9421/37 753)</td><td>1.0 (387/37 753)</td><td>4.1 (387/9421)</td></tr>
<tr><td>5 - 8</td><td>20.9 (1145/5487)</td><td>1.1 (59/5487)</td><td>5.2 (59/1145)</td></tr>
<tr><td colspan="4">Volumetry software analysis</td></tr>
<tr><td>No</td><td>32.4 (16 682/51 462)</td><td>1.1 (565/51 462)</td><td>3.4 (565/16 682)</td></tr>
<tr><td>Yes</td><td>17.5 (2084/11 910)</td><td>0.9 (104/11 910)</td><td>5.0 (104/2084)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
Recall rates, detection rates and PPV at jncident screen with LDCT
<table>
<tr><th>Category</th><th>Recall rate % (positive result/ participant)</th><th>Detection rate % (cancers detected/ participants)</th><th>PPV % (cancers detected/ positive results)</th></tr>
<tr><td colspan="4">Study type</td></tr>
<tr><td>Observational</td><td>28.4 (3322/11 709)</td><td>0.6 (71/11 709)</td><td>2.1 (71/3322)</td></tr>
<tr><td>RCT</td><td>18.1 (12 229/67 593)</td><td>0.8 (511/67 593)</td><td>4.2 (511/12 229)</td></tr>
<tr><td colspan="4">Cut-off size for solid non-calcified nodules</td></tr>
<tr><td>No</td><td>24.7 (3474/14 045)</td><td>0.6 (90/14 045)</td><td>2.6 (90/3474)</td></tr>
<tr><td>Yes</td><td>18.5 (12 077/65 257)</td><td>0.8 (492/65 257)</td><td>4.1 (492/12 077)</td></tr>
<tr><td colspan="4">Volumetry software analysis</td></tr>
<tr><td>No</td><td>23.0 (14 789/64 260)</td><td>0.7 (477/64 260)</td><td>3.2 (477/14 789)</td></tr>
<tr><td>Yes</td><td>5.1 (762/15 042)</td><td>0.7 (105/15 042)</td><td>13.8 (105/762)</td></tr>
</table>
Authors' Conclusion:
"These results highlight the value of using a cut-off size for nodules warranting further investigation with lower recall rates at prevalent screens, whereas the volumetric assessment software at incident screens results in lower recall rates and higher PPVs. " Page 781
</td></tr>
<tr><td>Bach,[6] 2012, USA</td><td>
Main Findings:
"Three RCTs have reported the impact of LDCT screening on lung cancer-specific mortality […] The NLST found that three annual rounds of screening (baseline, and 1and 2 years later) with LDCT resulted in a 20% relative decrease in deaths from lung cancer relative to CXR over a median of 6.5 years of follow-up (p=0.004) […] The considerably smaller ongoing DANTE and DLST studies each compare 5 annual rounds of LDCT screening to usual care; after a median of 34 and 58 months of follow-up, no statistically significant difference in lung cancer mortality was observed in either study (Dante: RR = 0.97, 95% CI 0.71–1.32, p = 0.84); (DLST: RR = 1.15, 95% CI 0.83–1.61, p=0.43)." Page 5 of 25

"In terms of potential harms of LDCT screening, across all trials and cohorts, about 20% of individuals in each round of screening had positive results requiring some degree of follow-up, while approximately 1% had lung cancer. There was marked heterogeneity in this finding and in the frequency of follow-up investigations, biopsies, and the percent of surgical procedures performed in those with benign lesions. Major complications in those with benign conditions were rare." Page 2 of 25

"The literature supports the conclusion that LDCT screening can lead to harm. It identifies a relatively high percentage of subjects with nodules (average ~20%), the vast majority of which are benign. The additional imaging that these nodules trigger increases radiation exposure. The rates of surgical biopsy are also variable (<1–4%) as are the percentage of surgical procedures performed for benign disease. The rate of major, and sometimes fatal, complications among those with benign conditions is low." Page 8 of 25
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
"LDCT screening may benefit individuals at an elevated risk for lung cancer, but uncertainty exists about potential harms and the generalizability of results." Page</td></tr>
<tr><td colspan="2">RCT</td></tr>
<tr><td>NLST,[7,12] 2013 and 2011, USA</td><td>Main Findings:
Outcomes at the first round of screening
<table>
<tr><th>Outcome</th><th>Screening with LDCT N = 26,715</th><th>Screening with CXR N = 26,724</th></tr>
<tr><td>Sensitivity (%)</td><td>93.8 (90.6 to 96.3)</td><td>73.5 (67.2 to 798.8)</td></tr>
<tr><td>Specificity (%)</td><td>73.4 (72.8 to 73.9)</td><td>91.3 (91.0 to 91.6)</td></tr>
<tr><td>Positive screen result (%)</td><td>27.3</td><td>9.2</td></tr>
<tr><td>PPV (%)</td><td>3.8 (3.3 to 4.2)</td><td>5.7 (4.8 to 57.4)</td></tr>
<tr><td>NPV (%)</td><td>99.9 (99.86 to 99.94)</td><td>99.8 (99.7 to 99.8)</td></tr>
<tr><td colspan="3">Values in parentheses represent the 95% confidence interval</td></tr>
</table>
Positive screen results (%) at each of the three rounds of screening
<table>
<tr><th>Screen</th><th>Screening with LDCT</th><th>Screening with CXR</th></tr>
<tr><td>First round (T0)</td><td>27.3</td><td>9.2</td></tr>
<tr><td>Second round (T1)</td><td>27.9</td><td>6.2</td></tr>
<tr><td>Third round (T2)</td><td>16.8</td><td>5.0</td></tr>
<tr><td>Over all three rounds</td><td>24.2</td><td>6.9</td></tr>
</table>
In the LDCT screening group 96.4% of the positive results and in the CRX group 94.5% of the positive results were false positives.

Authors' Conclusion:
"The rate of positive results was higher with low-dose CT screening than with radiographic screening by a factor of more than 3, and low-dose CT screening was associated with a high rate of false positive results…" Page 8 of 22 (NEJM)</td></tr>
<tr><td colspan="2">Economic studies</td></tr>
<tr><td>Roth,[13] 2015, USA</td><td>Main Findings:
Screening and diagnoses over five year results for base case
<table>
<tr><th>Parameter</th><th>LDCT screening</th><th>No screening</th><th>Difference between screening and no screening</th></tr>
<tr><td>Stage I or II (%)</td><td>52.1</td><td>22.6</td><td>29.5</td></tr>
<tr><td>Stage III (%)</td><td>23.5</td><td>33.9</td><td>-10.3</td></tr>
<tr><td>Stage IV (%)</td><td>24.4</td><td>43.5</td><td>-19.2</td></tr>
<tr><td>Total lung cancer diagnoses (n)</td><td>238,000</td><td>186,000</td><td>52,000</td></tr>
<tr><td>False-positive screen (%)</td><td>27.3</td><td>0</td><td>27.3</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
<table>
<tr><td>False negative screen (%)</td><td>0.04</td><td>0</td><td>0.04</td></tr>
<tr><td>Total screening episodes (n)</td><td>10,722,000</td><td>0</td><td>10,722,000</td></tr>
</table>
Fiscal impact over five years for base case
<table>
<tr><th>Parameter</th><th>LDCT screening</th><th>No screening</th><th>Difference between screening and no screening</th></tr>
<tr><td>Cost of screening episodes (billion US$)</td><td>4.3</td><td>0</td><td>4.3</td></tr>
<tr><td>Cost for diagnoses (billion US$)</td><td>1.3</td><td>0.3</td><td>1.0</td></tr>
<tr><td>Cost of cancer care (billion US$)</td><td>76.6</td><td>98.3</td><td>-21.7</td></tr>
<tr><td>Total expenditure (billion US$)</td><td>24.0</td><td>17.2</td><td>6.8</td></tr>
</table>
Authors' Conclusion:
"In conclusion, our analyses suggest that coverage of low-dose CT screening in Medicare enrollees age 55 to 77 years with ≥ 30–pack-year smoking history who are current smokers or quit in the last 15 years will result in more lung cancer diagnoses, a greater proportion of patient cases diagnosed at an early stage,
and increased Medicare expenditure. Although the degree of expenditure impact is uncertain, it is clear that the increased cost of conducting millions of screening examinations will greatly outweigh any potential cancer care savings from a stage shift. These results can inform planning efforts by Medicare administrators, contracted health care providers, and other stakeholders." Page 271
</td></tr>
<tr><td>Black,[15] 2014, USA</td><td>
Main Findings:
Incremental Cost-Effectiveness (ICER)
<table>
<tr><th rowspan="2">Category</th><th colspan="3">Screening strategy</th></tr>
<tr><th>LDCT</th><th>Radiography</th><th>No screening</th></tr>
<tr><td>Cost (US$)</td><td>3,074</td><td>1,911</td><td>1,443[a]</td></tr>
<tr><td>Life expectancy (life-year)</td><td>14.7386</td><td>14.7071</td><td>14.7071</td></tr>
<tr><td>QALY</td><td>10.9692</td><td>10.9491</td><td>10.9491</td></tr>
<tr><td>Incremental costs[b]</td><td>1,631</td><td>469</td><td>NA</td></tr>
<tr><td>Incremental life expectancy (life-year)</td><td>0.0316</td><td>0</td><td>NA</td></tr>
<tr><td>Incremental QALY</td><td>0.0201</td><td>0</td><td>NA</td></tr>
<tr><td>Cost per life-year (US$)</td><td>52,000 (34,000 to 106,000)</td><td>NA</td><td>NA</td></tr>
<tr><td>Cost per QALY(US$)</td><td>81,000 (52,000 to 186,000)[c]</td><td>NA</td><td>NA</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
[a]The cost of strategy with no screening included the cost of diagnosis and treatment of lung cancer without LDCT or radiographic screening
[b]Incremental costs are in reference to the strategy of no screening because the radiography strategy cost more but provided no incremental health benefit as compared with no screening.
[C] 95% confidence interval

Subgroup and sensitivity analyses
ICERs varied widely in subgroups categorized according to factors such as sex, age at entry and smoking status.
ICERs varied widely in sensitivity analyses by varying factors such as survival for Stage 1A non-small cell lung cancer, cost of screening with LDCT, and surgical mortality.
</td></tr>
<tr><td></td><td>
Authors' Conclusion:
"We estimated that screening for lung cancer with low-dose CT would cost $81,000 per QALY gained, but we also determined that modest changes in our assumptions would greatly alter this figure. The determination of whether screening outside the trial will be cost-effective will depend on how screening is implemented." Page 1794
</td></tr>
<tr><td>Tabata,[14] 2014, Japan</td><td>
Main Findings:
ICER for LDCT screening compared to chest radiography for smokers
<table>
<tr><th colspan="2">Patient category</th><th rowspan="2">Incremental cost per year of gained life expectancy (thousand yen)</th></tr>
<tr><th>Gender</th><th>Age (years)</th></tr>
<tr><td rowspan="4">Male</td><td>55 to 59</td><td>1,400</td></tr>
<tr><td>60 to 64</td><td>679</td></tr>
<tr><td>65 to 69</td><td>550</td></tr>
<tr><td>70 to 74</td><td>268</td></tr>
<tr><td rowspan="4">Female</td><td>55 to 59</td><td>1,942</td></tr>
<tr><td>60 to 64</td><td>1,524</td></tr>
<tr><td>65 to 69</td><td>1,322</td></tr>
<tr><td>70 to 74</td><td>983</td></tr>
</table>
Sensitivity analysis
<table>
<tr><th rowspan="3">Patient category</th><th colspan="4">Incremental cost per one year life expectancy gained (thousand yen) with</th></tr>
<tr><th rowspan="2">Rate of requiring thorough examinations (%)</th><th colspan="3">Cost of the examination (yen)</th></tr>
<tr><th>5,000</th><th>10,000</th><th>15,000</th></tr>
<tr><td rowspan="2">Male of age 55 to 59 years</td><td>5</td><td>442</td><td>1,092</td><td>1,743</td></tr>
<tr><td>35</td><td>1,223</td><td>1,874</td><td>2,534</td></tr>
<tr><td rowspan="2">Male of age 60 to 64 years</td><td>5</td><td>185</td><td>540</td><td>895</td></tr>
<tr><td>35</td><td>611</td><td>966</td><td>1,322</td></tr>
<tr><td rowspan="2">Female of age 55 to 59 years</td><td>5</td><td>622</td><td>1,506</td><td>2,389</td></tr>
<tr><td>35</td><td>1,682</td><td>2,566</td><td>3,449</td></tr>
<tr><td rowspan="2">Female of age 70 to 74 years</td><td>5</td><td>239</td><td>720</td><td>1,202</td></tr>
<tr><td>35</td><td>817</td><td>1,298</td><td>1,779</td></tr>
</table>
ICERs varied widely in sensitivity analyses on varying factors such as rate of requiring thorough examination and cost of the examination
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
"In conclusion, LDCT could be introduced for male and female smokers aged 55 and 65 (or 70) years or older, respectively. Furthermore, the present study elucidates the requirements for the introduction of LDCT cancer screening including the age, cost of LDCT screening, and interval between screening." Page 21</td></tr>
<tr><td>Wattson,[16] 2014, USA</td><td>Main Findings:
ICER for LDCT screening compared to no screening for different HL survivor groups
<table>
<tr><th colspan="2">Patient group</th><th rowspan="2">ICER (US$/QALY)</th></tr>
<tr><th>Smoking status, age at HL diagnosis</th><th>Gender, radiation therapy</th></tr>
<tr><td rowspan="4">Smoker, HL at age 25 years</td><td>Male, mantle (35 Gy)</td><td>34,841</td></tr>
<tr><td>Male, IFRT (20 Gy)</td><td>78,890</td></tr>
<tr><td>Female, mantle (35 Gy)</td><td>30,250</td></tr>
<tr><td>Female, IFRT (20 Gy)</td><td>74,476</td></tr>
<tr><td rowspan="4">Smoker, HL at age 35 years</td><td>Male, mantle (35 Gy)</td><td>11,252</td></tr>
<tr><td>Male, IFRT (20 Gy)</td><td>32,836</td></tr>
<tr><td>Female, mantle (35 Gy)</td><td>11,908</td></tr>
<tr><td>Female, IFRT (20 Gy)</td><td>40,114</td></tr>
<tr><td rowspan="4">Nonsmoker, HL at age 25 years</td><td>Male, mantle (35 Gy)</td><td>1,037,267</td></tr>
<tr><td>Male, IFRT (20 Gy)</td><td>1,186,770</td></tr>
<tr><td>Female, mantle (35 Gy)</td><td>Dominated</td></tr>
<tr><td>Female, IFRT (20 Gy)</td><td>Dominated</td></tr>
<tr><td rowspan="4">Nonsmoker, HL at age 35 years</td><td>Male, mantle (35 Gy)</td><td>139,455</td></tr>
<tr><td>Male, IFRT (20 Gy)</td><td>795,685</td></tr>
<tr><td>Female, mantle (35 Gy)</td><td>243,121</td></tr>
<tr><td>Female, IFRT (20 Gy)</td><td>Dominated</td></tr>
<tr><td colspan="3">Willingness to pay threshold (WTPT) = US$ 50,000/QALY</td></tr>
</table>
Sensitivity analysis using low and high values of model parameter compared with Baseline Model
<table>
<tr><th colspan="2">Model parameters</th><th rowspan="2">ICER (US$/QALY)</th></tr>
<tr><th>Category</th><th>Value</th></tr>
<tr><td>Baseline Model</td><td>baseline</td><td>34,841</td></tr>
<tr><td rowspan="2">Annual lung cancer incidence</td><td>0.5 X baseline rate</td><td>131,639</td></tr>
<tr><td>2.0 X baseline rate</td><td>7,422</td></tr>
<tr><td rowspan="2">Lung cancer mortality rate</td><td>0.5 X baseline rate</td><td>18,019</td></tr>
<tr><td>2.0 X baseline rate</td><td>183, 711</td></tr>
<tr><td rowspan="2">Non-lung cancer mortality rate</td><td>0.5 X baseline rate</td><td>24,919</td></tr>
<tr><td>2.0 X baseline rate</td><td>53,120</td></tr>
<tr><td rowspan="2">Rate of false-positive LDCT</td><td>0.5 X baseline rate</td><td>22,661</td></tr>
<tr><td>2.0 X baseline rate</td><td>66,802</td></tr>
<tr><td rowspan="2">Length of disutility time from false-positive LDCT</td><td>0.5 X baseline rate</td><td>29,775</td></tr>
<tr><td>2.0 X baseline rate</td><td>52,813</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
"HL survivors are an important high-risk population that may benefit from screening, especially those treated in the past with large radiation fields including mantle or involved-field RT. Screening may be cost effective for all smokers but possibly not for non-smokers despite a small life expectancy benefit." Page 345</td></tr>
<tr><td rowspan="2">Shmueli,[2] 2013, Israel</td><td>Main Findings:
In the base case scenario, the incremental cost of screening US$86.4704 and the incremental effectiveness is 0.059082 QALY. The cost per QALY gained as a result of screening was US$1464.Sensitivity analysis showed that the result was robust.</td></tr>
<tr><td>Authors' Conclusion:
"In conclusion, our analysis suggests that LDCT lung cancer screening in Israel may be associated with a relatively low cost per QALYs gained by screening, and may deserve inclusion in the public list of health services. Further research should be con ducted, however, to confirm these findings with more recent, larger, and more reliable datasets, and to expand the analysis to include follow-up screenings. Such results will inform policy- makers and will contribute to policy decisions regarding the allocation of health care resources to LDCT screening." Page 931</td></tr>
<tr><td rowspan="2">Villanti,[17] 2013, USA</td><td>Main Findings:
A hypothetical cohort 18 million adults in the age range 50 and 64 years with ≥ 30pack years of smoking history were considered. Cost for the lung cancer screening was US$ 27.8 million over 15 years and the QALY gained was 985,284 resulting in a cost-utility ratio of US$28,240 per QALY gained. Addition of smoking cessation programs to the screening program increased both cost and QALY gained and resulted in cost-utility ratios varying between US$16,198 per QALY and 23,185 QALY gained depending on the choice of the smoking cessation program. Parameters were varied and sensitivity analyses were conducted and the screening with LDCT remained cost-effective.</td></tr>
<tr><td>Authors' Conclusion:
"The findings of this study indicate that repeat annual lung cancer screening in a high risk cohort of adults aged 50–64 is highly cost-effective. Offering smoking cessation interventions with the annual screening program improved the cost-effectiveness of lung cancer screening between 20% and 45%. The cost-utility ratios estimated in this study were in line with other accepted cancer screening interventions and support inclusion of annual LDCT screening for lung cancer in a high risk population in clinical recommendations." Page 1 of 11</td></tr>
<tr><td>Goulart,[18] 2012, USA</td><td>Main Findings:
<table>
<tr><th>Parameter</th><th>Screening rate 50%</th><th>Screening rate 75%</th></tr>
<tr><td>Number screened per year (n)</td><td>1,736,844</td><td>2,605,266</td></tr>
<tr><td>Number needed to screen to avoid one lung cancer death (n)</td><td>320</td><td>320</td></tr>
<tr><td>Additional lung cancer deaths avoided per year by screening (n)</td><td>5,428</td><td>8,141</td></tr>
</table></td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion
	Additional cost of screening with LDCT (US$ million) | 1,303.0 | 1,970.8 Additional cost per lung cancer death avoided (2011 US$) | 240, 081 | 242,074 n = number of persons "Using nationally representative estimates of the prevalence of current and former smokers, data from the NLST, and Medicare expenditures, the authors estimated that LDCT screening for lung cancer will increase national annual healthcare expenditures by US$1.3 to US$2.0 billion, depending on adherence. These expenditures represent a 12% to 19% increase over the current US$12.1 billion spent annually for lung cancer care in the United States." Page 274
	Authors' Conclusion: "Implementation of LDCT screening will add $1.3 to $2.1 billion in annual national health care expenditures for screening rates of 50% ton75%, respectively. LDCT screening has the potential to avoid more than 8000 premature lung cancer deaths per year, but the true value of this intervention awaits the results of formal cost-effectiveness analysis of long-term costs and outcomes compared with no screening. Efforts to reduce false-positive screening results and adherence to diagnostic algorithms after a positive LDCT screening test will likely reduce the impact of LDCT screening on health care expenditures." Pages 274 to 275

CI = confidence interval, CT = computed tomography, CXR = chest X-ray, DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology, DLST = Danish lung cancer screening trial, HL = Hodgkin's lymphoma, ICER = incremental cost-effectiveness ratio, IFRT = involved-field radiation therapy, LDCT = low-dose computed tomography, NLST = National Lung Screening Trial, NPV = negative predictive value, OR = odds ratio, PPV = positive predictive value, QALY = quality-adjusted life-year, RCT = randomized controlled trial, US = United States

APPENDIX 8: Guidelines and Recommendations

Guideline Society/ Author, Year, Country, A	Recommendations
USPSTF,[19] 2014 USA; Summary[26]	"The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. (B recommendation)" Page 330
ACCP,[20] 2013 USA	"For smokers and former smokers who are age 55 to 74 and who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with LDCT should be offered over both annual screening with CXR or no screening, but only in settings that can deliver the comprehensive care provided to NLST participants (Grade 2B)." page e85s "For individuals who have accumulated fewer than 30 pack-years of smoking or are either younger than age 55 or older than 74, or individuals who quit smoking more than 15 years ago, and for individuals with severe comorbidities that would preclude potentially curative treatment and/or limit life expectancy, we suggest that CT screening should not be performed (Grade 2C)." page e85s
ACS,[21] 2013, USA	"Clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about lung cancer screening with patients aged 55 years to 74 years who have at least a 30-pack-year smoking history, currently smoke, or have quit within the past 15 years, and who are in relatively good health. Core elements of this discussion should include the following benefits, uncertainties, and harms of screening: • Benefit: Screening with LDCT has been shown to substantially reduce the risk of dying from lung cancer. • Limitations: LDCT will not detect all lung cancers or all lung cancers early, and not all patients who have a lung cancer detected by LDCT will avoid death from lung cancer. • Harms: There is a significant chance of a false-positive result, which will require additional periodic testing and, in some instances, an invasive procedure to determine whether or not an abnormality is lung cancer or some non-lung cancer related incidental finding. Fewer than 1 in 1000 patients with a false-positive result experience a major complication resulting from a diagnostic workup. Death within 60 days of a diagnostic evaluation has been documented, but is rare and most often occurs in patients with lung cancer. • Smoking cessation counseling constitutes a high priority for clinical attention for patients who are currently smoking. Current smokers should be informed of their continuing risk of lung cancer, and referred to smoking cessation programs. Screening should not be viewed as an alternative to smoking cessation. • Eligible patients should make the screening decision together with their health care provider. Helping individuals to clarify their personal values can facilitate effective decision-making:

Guideline Society/ Author, Year, Country, A	Recommendations
	• Individuals who value the opportunity to reduce their risk of dying from lung cancer and who are willing to accept the risks and costs associated with having a LDCT and the relatively high likelihood of the need for further tests, even tests that have the rare but real risk of complications and death, may opt to be screened with LDCT every year. • Individuals who place greater value on avoiding testing that carries a high risk of false-positive results and a small risk of complications, and who understand and accept that they are at a much higher risk of death from lung cancer than from screening complications, may opt not to be screened with LDCT. • Clinicians should not discuss lung cancer screening with LDCT with patients who do not meet the above criteria. If lung cancer screening is requested, these patients should be informed that at this time, there is too much uncertainty regarding the balance of benefits and harms for individuals at younger or older ages and/ or with less lifetime exposure to tobacco smoke and/or with sufficiently severe lung damage to require oxygen (or other health-related NLST exclusion criteria), and therefore screening is not recommended. • Adults who choose to be screened should follow the NLST protocol of annual LDCT screening until they reach age 74 years. • CXR should not be used for cancer screening. • Wherever possible, adults who choose to undergo lung screening preferably should enter an organized screening program at an institution with expertise in LDCT screening, with access to a multidisciplinary team skilled in the evaluation, diagnosis, and treatment of abnormal lung lesions. If an organized, experienced screening program is not accessible, but the patient strongly wishes to be screened, they should be referred to a center that performs a reasonably high volume of lung CT scans, diagnostic tests, and lung cancer surgeries. If such a setting is not available and the patient is not willing or able to travel to such a setting, the risks of cancer screening may be substantially higher than the observed risks associated with screening in the NLST, and screening is not recommended. Referring physicians should help their patients identify appropriate settings with this expertise." Page 11, 12 of 18
Cancer Care Ontario,[23] 2013, Canada; Summary[24]	Recommendation 1: "Screening for lung cancer with LDCT is recommended in high-risk populations defined as persons 55 to 74 years of age with a minimum smoking history of ≥30 pack-years who currently smoke or have quit within the past 15 years and are disease free at the time of screening." Page 6 Recommendation 2: Positive Result and Follow-up "□ Screening modality: Screening for lung cancer should be done using an LDCT multi-detector scanner with the following parameters: 120 to 140 peak kilovoltage (kVp), 20 to 60 milliampere seconds (mAs), with an average effective dose ≤1.5 millisieverts (mSv). □ Collimation should be ≤2.5 mm. □ Definition of a positive result: A nodule size of ≥5 mm found on LDCT indicates a positive result and warrants a 3-month follow-up CT. Nodules ≥15 mm should undergo immediate further diagnostic procedures to rule out definitive malignancy. □ Appropriate follow-up of a positive result: Follow-up CT of a nodule should be done at 3 months as a limited LDCT scan (i.e., only a slab covering the nodule will be scanned, not the entire chest). The Lung Cancer Diagnosis Pathway should be consulted for guidance on clinical work-up." Page 7

Guideline Society/ Author, Year, Country, A	Recommendations
	Recommendation 3: "Persons at high risk for lung cancer should commence screening with an initial LDCT scan followed by annual screens for 2 consecutive years, and then once every 2 years after each negative (-ve) scan." Page 9
AATS,[22] 2012, USA	"1. Annual lung cancer screening with LDCT for smokers and former smokers with 30 pack-year history of smoking from ages 55 to 79 y. 2. Long-term lung cancer survivors should have annual LDCT to detect second primary lung cancer until the age of 79 y. 3. Annual lung cancer screening with LDCT for smokers and former smokers aged 50 to 79 y with a 20 pack-year history of smoking and additional comorbidity that produces a cumulative risk of developing lung cancer of ≥ 5% over the following 5 y. 4. Lung cancer screening and successful treatment of early-stage lung cancer by a subspecialty qualified team, including thoracic surgeons, thoracic radiologists, pulmonologists, oncologists, and pathologists. 5. Develop a web-based application for patient self-risk assessment. 6. Continue AATS engagement with other specialty societies to develop and refine future screening guidelines." Page 27

AATS = American Association of Thoracic Surgery, ACS = American Cancer Society, ACCP = American College of Chest Physicians, CCO = Cancer Care Ontario, LDCT = low-dose computed tomography, USPSTF = United States Preventive services Task Force, y = year