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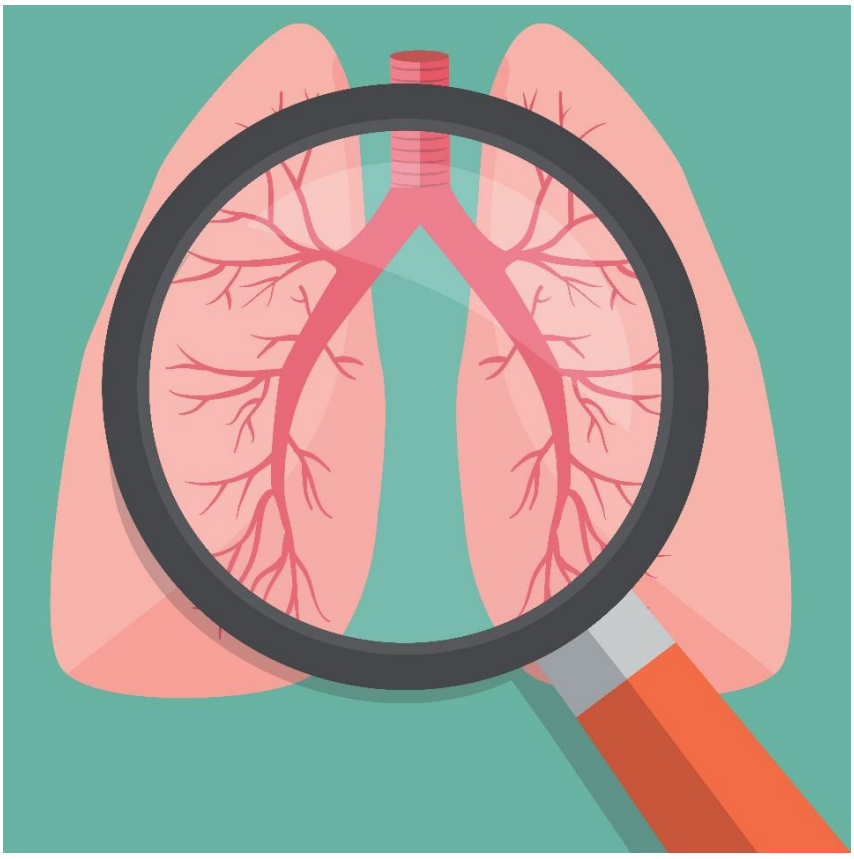
Lung Cancer Screening in Risk Groups



A review-update of the economic evidence (Part II)

Final Report

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A review-update of the economic evidence (Part II)

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List of abbreviations

AUD .....Australian Dollar
BIA .....Budget Impact Analysis
BMI .....Body Mass Index
CA .....Cost-Analysis
CAD .....Canadian Dollar
CBA.....Cost-Benefit Analysis
CEA.....Cost-Effectiveness Analysis
CISNET .....Cancer Intervention and Surveillance Modelling Network
CMA.....Cost-Minimisation Analysis
CMS .....Centres for Medicare & Medicaid Services
COPD.....Chronic obstructive pulmonary disease
COSMOS .....Continuing Observation of Smoking Subjects
CT.....Computed Tomography
CUA .....Cost-Utility Analysis
DALY.....Disability Adjusted Life Year
DRG .....Diagnostic Related Group
ERS .....European Respiratory Society
ESR .....European Society of Radiology
EUR.....Euro
EQ-5D .....EuroQol 5 Dimensions
GBP .....Great Britain Pounds
GP.....General Practitioner
HMO .....Health Maintenance Organisation
HrQoL.....Health-related Quality of Life
HTA .....Health Technology Assessment
ICER .....Incremental Cost-Effectiveness Ratio
INMB .....Incremental Net Monetary Benefit
LDCT.....Low Dose Computed Tomography
LHC..... Lung Health Check
LYG ..... Life Year Gained
MISCAN ..... MIcrosimulation SCreening Analysis
MRI..... Magnetic Resonance Imaging
NELSON..... Dutch-Belgian Randomized Lung Cancer Screening Trial
NGO..... Non-Governmental Organisation
NHI..... National Health Insurance
NHS ..... National Health Service
NICE ..... National Institute for Health and Care Excellence
NLST..... National Lung Screening Trial
NPV ..... Net Present Value
PanCan..... Pan-Canadian Early Detection of Lung Cancer Study
PET-CT ..... Positron Emission Tomography–Computed Tomography
PLCO..... Prostate, Lung, Colorectal, and Ovarian Cancer Trial
PSS..... Personal Social Services
QALY..... Quality-Adjusted Life Year
RADS..... Lung CT screening reporting and data system
ROI ..... Return on Investment
SEER ..... Surveillance, Epidemiology, and End Results Medicare database
SF-36..... Short Form 36
UK..... United Kingdom
UKLS..... UK Lung Cancer Screening Trial
USA..... United States of America
USD ..... United States Dollar
USPSTF ..... U.S. Preventive Services Task Force

Zusammenfassung

Hintergund

Lungenkrebs ist die häufigste krebsbedingte Todesursache in Österreich

Lungenkrebs ist in Österreich für rund 10,8 % aller neudiagnostizieren Krebserkrankungen bei Frauen und für rund 12,9 % bei Männern verantwortlich. Ebenso stellt die Erkrankung die häufigste krebsbedingte Todesursache in Österreich, mit einem Anteil von rund 16,6 % bei Frauen und 20,9 % bei Männern dar. Die meisten Lungenkrebserkrankungen werden dem Rauchen zugeordnet, wobei jedoch auch arbeitsplatzbedingte Risikofaktoren wie Radon-, Feinstaub- oder Asbestbelastungen zu nennen sind.

neuere Studien zeigen positive Effekte von Lungenkrebs-Screening mit LDCT

Ergebnisse von Studien wie dem National Lung Screening Trial (NLST) oder dem Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) scheinen eine Reduktion der Lungenkrebsmortalität (wenngleich nicht notwendigerweise der Gesamtmortalität) durch Lungenkrebs-Screening mittels Low Dose Computed Tomography (LDCT) zu bestätigen. Seit der Veröffentlichung dieser Ergebnisse wurden zahlreiche ökonomische Evaluationen von LDCT-Screening für Lungenkrebs publiziert.

Ziele

Updade bestehender Evidenz zu ökonomischen Evaluationen von Lungenkrebs-Screening mittels LDCT mit Schwerpunkt auf Studienmethodik und Kostenfaktoren

Dieser systematische Review hat zum Ziel, die gesundheitsökonomische Evidenz im Sinne der Kosten-Effektivität, dem Kosten-Nutzwert sowie den Budgetfolgen von Lungenkrebs-Screening mittels LDCT versus ‚kein Screening' bzw. ‚Screening mittels anderer bildgebender Verfahren' für Personen mit erhöhtem Risiko jedoch ohne Verdacht auf bzw. bestätigter Lungenkrebsdiagnose zusammenzufassen und auf den neuesten Stand zu bringen.

Die Forschungsfragen dieses Reviews beziehen sich auf die Methoden, die in ökonomischen Evaluationen zur Bewertung der Kosten von Lungenkrebs-Screening angewandt wurden, auf relevante Kostenfaktoren für Lungenkrebs-Screening, sowie auf die Ergebnisse ökonomischer Evaluationen im Sinne von Kosten-Effektivität, Kosten-Nutzwert und Budgetfolgen. Darüber hinaus wird in diesem Bericht auch darauf eingegangen, ob eine ökonomische Evaluation für Österreich sinnvoll ist, und falls ja, welche Methoden zur Kostenbewertung von Lungenkrebs-Screening mittels LDCT hierfür angewandt werden sollten.

Methoden

systematischer Review zur Kosten-Effektivität, Kosten-Nutzwert und den Budgetfolgen von LDCT-Lungenkrebs-Screening

Der Literaturüberblick beruht auf einer systematischen Datenbankrecherche von sechs Publikationsdatenbanken sowie einer ausführlichen händischen Suche nach weiteren relevanten Publikationen. Die Datenextrahierung erfolgte mittels eines vorab entwickelten und getesteten Extraktionsformulars. Mit Hilfe dieses Formulars wurden neben allgemeiner Studienmerkmale insbesondere die angewandten gesundheitsökonomischen Methoden, maßgebliche Kostenfaktoren, die bei der ökonomischen Bewertung von Lungenkrebs-Screening mittels LDCT zu berücksichtigen sind und schließlich auch die Ergebnisse der eingeschlossenen Studien extrahiert und tabellarisch zusammengefasst. Ein Transfer der Ergebnisse auf den österreichischen Kontext fand nicht statt, jedoch wurden Methoden der eingeschlossenen Studien im Sinne ihrer Anwendbarkeit auf den österreichischen Kontext ausführlich diskutiert.

Ergebnisse

13/59 begutachteten Volltexte in qualitative Synthese inkludiert

Von 561 Referenzen wurden 59 Studien im Volltext evaluiert. Insgesamt wurden 25 Studien auf der Grundlage der vordefinierten Einschlusskriterien inkludiert, allerdings wurden nur 13 der 25 Studien für die qualitative Synthese berücksichtigt, da diese in früheren systematischen Übersichten nicht bewertet wurden.

Ergebnisse ökonomischer Evaluationen nicht eindeutig

Base-Case-Analysen der eingeschlossenen Studien lassen keine eindeutige Aussage hinsichtlich der Kosten-Effektivität bzw. dem Kosten-Nutzwert der Intervention zu. Während sechs der eingeschlossenen Studien zu dem Schluss kamen, Lungenkrebs-Screening mittels LDCT sei im Vergleich der von den Autor*innen gewählten Schwellenwerte kosteneffektiv, so kamen zwei weitere Studien zu dem gegenteiligen Ergebnis. Fünf Studien berichteten gemischte Ergebnisse, ohne eindeutig die Kosten-Effektivität von LDCT-Screening zu bestätigen oder zu widerlegen. Dieses Ergebnis deckt sich auch mit anderen publizierten Reviews zum Thema.

erhebliche Variabilität in Programm-spezifikationen, z. B. bzgl. Screening-Intervallen

jährliches Screening womöglich effektiver aber auch kostspieliger im Vergleich zu zweijährigen Screening-Intervallen

Jene Studien, die unterschiedliche Screening-Szenarios testeten, kamen überwiegend zu dem Ergebnis, dass ein zweijähriges Screening-Intervall eine geringere (also vorteilhaftere) Kosten-Nutzwert-Relation als ein einjähriges Intervall aufweist, jeweils verglichen mit ‚kein Screening'. Dabei ist anzumerken, dass kürzere Intervalle zwar teurer sind, jedoch auch einen höheren Gesundheitsnutzen aufweisen, sodass ein angemessenes Intervall für Österreich im Vergleich zur jeweiligen gesellschaftlichen Zahlungsbereitschaft für die Intervention im Rahmen einer ökonomischen Evaluation gefunden werden müsste. Was die Einschlusskriterien betrifft, so lag das Screening-Alter in den meisten Studien zwischen 55 und 75 Jahren, wobei der Einschluss älterer Teilnehmer*innen (über 75) wohl einen geringeren Gesundheitsnutzen aufweist, der sich nicht durch die zusätzlichen Kosten rechtfertigen lässt. Sensitivitätsanalysen der jeweiligen Studien stellten darüber hinaus die Relevanz der unteren Altersgrenze für Screening fest, sodass die optimalen Altersgrenzen für Österreich im Rahmen einer ökonomischen Evaluation ermittelt werden müssten.

Methoden, Komponenten und Faktoren, die zur Erhebung der Kosten von LDCT-Screening zu berücksichtigen sind

Grundsätzliche Kostenkomponenten in ökonomischen Evaluationen für Lungenkrebs-Screening mittels LDCT sind die Screening-Kosten, Behandlungskosten, sowie Kosten für unterstützende und palliative Behandlung und Pflege. Neben generellen methodischen Studieneigenschaften, wie etwa die ökonomische Perspektive, Zeithorizont und Diskontsätze sowie Methoden und Daten zur Kostenerhebung, gehören zu den relevanten Kostenfaktoren in ökonomischen Evaluation von Lungenkrebs-Screening mittels LDCT unter anderem die Teilnehmer*innenrate an Screening-Programmen, Sensitivität und Spezifizität von LDCT, die Effekte von unklaren bzw. nicht eindeutigen Screening-Ergebnissen, zufällige Diagnosen weiterer Erkrankungen, die Kosten (und Gesundheitseffekte) von Komplikationen im Zusammenhang mit Screening, Diagnose, und Behandlung sowie die Auswirkungen von Length-Bias, Lead-Time-Bias und potentieller Überdiagnose.

Diskussion

methodische Faktoren für eine Evaluation von LDCT-Screening in Österreich, z. B.

Komparator: „kein Screening“

Risikobewertung

Eine ökonomische Evaluation für Österreich sollte die Perspektive des österreichischen Gesundheitssystems einnehmen und LDCT-Screening gegen 'kein Screening' vergleichen. Risikofaktoren (wie Anzahl der gerauchten Packungen pro Jahr, Zeit seit der Raucherentwöhnung, relevante Belastungen am Arbeitsplatz, etc.) sollten ebenso in einer Studie für Österreich systematisch analysiert werden. Dabei könnten auch validierte Instrumente zur Risikobewertung zum Einsatz kommen, wobei existierende Studien diesbezüglich zu gemischten Ergebnissen kommen. Die Annahmen zur Identifikation und Rekrutierung von Teilnehmner*innen sollten sich an existierenden Screening-Programmen in Österreich orientieren, das zur Evaluation stehende Programm unter Berücksichtigung bereits existierender Kapazitäten evaluiert werden und angemessene Annahmen hinsichtlich der Beteiligungsrate sowie entstehender Kosten getroffen werden.

Lebenszeithorizont, zumindest jedoch 25 Jahre

Diskontierung von Kosten & Effekten mit 5,0 % im Base-Case

Für ein österreichisches Modell wäre es empfehlenswert, wenn der Zeithorizont einer ökonomischen Evaluation die Lebenszeit der eingeschlossenen Personengruppe umfassen würde, zumindest jedoch 25 Lebensjahre. Weiters wird ein Diskontsatz von 5,0 % in Anlehnung an österreichische Guidelines zur gesundheitsökonomischen Evaluation für den Base-Case empfohlen, jedoch sollten Sensitivitätsanalysen zwischen 3,0 % und 10,0 % durchgeführt und berichtet werden.

klinische Effekte als QALYs & gewonnene Lebensjahre

Health State Utilities mittels EQ-5D

Parameter für klinische Effekte sollten auf der quantitativen Synthese existierender experimenteller Studien beruhen, wie sie in Teil I dieses Projektes systematisch erfasst wurden. Darüber hinaus wird empfohlen, Gesundheitseffekte in qualitätsadjustierten Lebensjahren (engl. QALYs) zu bemessen, jedoch auch ‚ungewichtet' als gewonnene Lebensjahre zu berichten. Health State Utilities sollten mit dem EuroQol-5D Instrument bemessen werden, wobei wegen des derzeitigen Fehlens österreichsicher Value-Sets auf andere Länder, wie z. B. Deutschland zurückgegriffen werden müsste. Es wird empfohlen, Heterogenität und Unsicherheit in angemessenen Sensitivitäts- und Szenarioanalysen zu erörtern.

Kosten der Behandlung & Palliativpflege nach Krebsstadien differenziert

mögliche Kostenfaktoren, z. B. falsch-positive bzw. falsch-negative Resultate, Überdiagnose

Administrative Datensätze bieten sich an, um Informationen bezüglich des entstehenden Ressourcenverbrauchs und der Kosten sowohl im niedergelassenen als auch im stationären Bereich zu erheben, und Kostenwerte sollten sich auf österreichische Tarife stützen. Der durch Lungenkrebs-Screening erhoffte Stage-Shift erfordert eine nach Krebsstadium differenzierte Betrachtung der Behandlungskosten sowie auch der Kosten unterstützender und ggf. auch palliativer Behandlung und Pflege. Die Auswirkungen von LDCT-Sensitivität und -Spezifität auf die Kosten (und Outcomes) des Screenings sollten in einem österreichischen Modell explizit erörtert werden. Ebenso wären die Auswirkungen unklarer Testergebnisse, Komplikationen bei diagnostischen Verfahren, die mögliche Diagnose anderer Erkrankungen (‚incidental findings') sowie Lead-time Bias, Length-Bias und mögliche Überdiagnosen zu testen.

existierendes oder neues Modell für Österreich?

Bevor eine ökonomische Evaluation für Österreich stattfinden kann, wäre jedoch grundsätzlich die Frage zu klären, ob ein de novo Modell für Österreich notwendig ist, oder ein existierendes Modell auf den österreichischen Kontext angepasst werden könnte.

Schlussfolgerungen

Lungenkrebs-Screening ist eine kostenintensive Intervention

Lungenkrebs-Screening ist zweifelsohne eine kostenintensive Intervention, deren Einführung nicht nur von der zu erwartenden Kosten-Effektivität, sondern auch den möglichen Budgetfolgen abhängt. Eine nationale Umsetzung würde also sowohl eine entsprechende Zahlungsbereitschaft als auch eine hinreichende finanzielle Leistungsfähigkeit auf System-Ebene voraussetzen, was Lungenkrebs-Screening tendenziell zu einer Intervention ressourcenstarker Gesundheitssysteme macht.

derzeit keine eindeutigen Aussagen zur Kosten-Effektivität der LDCT-Lungenkrebs-Screening-Programme möglich

Aufgrund der erheblichen Diskrepanz sowohl in Studienmethodik als auch deren Ergebnissen ist es derzeit jedoch nicht möglich, eindeutige Aussagen zur Kosten-Effektivität von Lungenkrebs-Screening mittels LDCT zu treffen. Die eingeschlossenen Studien zeichnen sich vor allem durch unterschiedliche Einschlusskriterien, Programmspezifikationen, Datenquellen, Modelle sowie der Betrachtung unterschiedlicher Screening-spezifischer Kostenfaktoren aus. All dies kann die Kosten-Effektivität einer Studie erheblich beeinflussen. Darüber hinaus kamen bei der Interpretation der Studienergebnisse jeweils unterschiedliche Zahlungsbereitschafts-Schwellenwerte zum Einsatz, was die Einschätzung der Kosten-Effektivität von LDCT-Screening im österreichischen Kontext zusätzlich erschwert.

Jährliches Screening effektiver aber auch kostspieliger als zweijährige Screening-Intervalle

Tendenziell lässt sich sagen, dass jährliches Screening womöglich effektiver im Vergleich zu längeren Screening-Intervallen ist, aufgrund der höheren Kosten jedoch auch zu einer höheren (nachteiligen) Kosten-Nutzwert-Relation führt, und daher sowohl eine höhere Zahlungsbereitschaft voraussetzen als auch stärkere Budgetfolgen mit sich bringen würde.

ökonomische Evaluation für Österreich dringend erforderlich

Eine ökonomische Evaluation für den österreichischen Kontext wird empfohlen, sowohl im Sinne des Kosten-Nutzwerts als auch im Sinne der Budgetfolgen der Intervention. Zukünftige Forschung sollte sich daher auch der Spezifizierung österreichischer Value-Sets für das EuroQol-5D Instrument, sowie der Bemessung eines angemessenen Kosten-Effektivitäts-Schwellenwertes widmen.

Executive Summary

Background

lung cancer is the most common cancer-related cause of death in Austria

In Austria, lung cancer accounts for around 10.8% of all newly diagnosed cancers in women and 12.9% in men, and it is responsible for 16.6% and 20.9% of cancer-related deaths in women and men respectively, making it the most frequent cancer-related cause of death in Austria. Most lung cancer cases are attributed to smoking, but occupational factors such as radon, asbestos or particulate matter exposure may also increase the risk for developing the disease.

recent studies showed positive effects of lung cancer screening with LDCT

Results from studies, such as the National Lung Screening Trial (NLST) or the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) seem to confirm a potential relative lung-cancer mortality reduction (although not necessarily overall mortality) from low dose computed tomography (LDCT)-screening for lung cancer. Since then, a considerable body of new evidence emerged on the cost-effectiveness of LDCT-screening for lung cancer.

Aim and objectives

project aim: update of existing evidence on economic evaluations of lung cancer screening using LDCT with focus on study methodology and cost-factors

This systematic review aims to provide an update of the evidence on the cost-effectiveness, cost-utility and budget impact of lung cancer screening using LDCT versus no screening or screening with other imaging technologies in adult persons without confirmed or suspected lung cancer but at elevated risk.

The research questions of this review relate to the methods that have been used to estimate the cost of lung cancer screening; the relevant cost-factors of lung cancer screening; and the results of existing economic evaluations of lung cancer screening in terms of cost-effectiveness, cost-utility, and budget impact. The exercise also aims to inform whether an economic evaluation for Austria is warranted and if so, which methods should be adopted for assessing the cost of LDCT-screening for lung cancer in Austria.

Methods

a systematic review of the cost-effectiveness, cost-utility and budget impact of LDCT lung cancer screening

A systematic literature review of international studies reporting on the cost-effectiveness, cost-utility and/or budget impact of lung cancer screening using LDCT was performed in six databases. The review was based on a systematic search for peer-reviewed economic evaluations on lung cancer screening with LDCT in relevant publication databases, complemented with a thorough hand search for relevant references in key publications. The extraction of data from includable studies was based on a previously developed and pilot-tested data extraction form. Key methods used in available studies to estimate the cost of lung cancer screening with LDCT, relevant cost-factors as reported in health economic evaluations of lung cancer screening using LDCT, and cost-effectiveness, cost-utility, and budget impact estimates from international studies were tabulated and discussed, but without transferring results to the Austrian context.

Results

13/59 full-texts included in qualitative synthesis

From a total of 561 references, 59 articles were reviewed in full-text. A total of 25 studies were included based on the predefined inclusion criteria; however only 13 of the 25 studies were considered for the qualitative synthesis as they had not been assessed in previous systematic reviews.

heterogeneous cost-effectiveness results of LDCT lung cancer screening

Base-case results of economic evaluations on LDCT-screening provide a mixed picture on the cost-effectiveness of the intervention. Whilst six studies were in support and reported ICERs lower than the cost-effectiveness threshold applied by their respective authors, two studies were not in support of the intervention, and another five studies reported mixed results for LDCT lung cancer screening. This mixed result is also in accord with other systematic reviews on the cost-effectiveness of lung-cancer screening with LDCT.

considerable variability in program specifications, e.g., screening intervals & age groups

annual screening may be more effective, but biennial screening may be more cost-effective

Whilst annual screening appears to be more effective compared to longer screening-intervals, it is also more costly, which is why studies comparing different screening scenarios with respect to screening intervals generally found biennial screening to be more cost-effective than annual screening. Age groups tested in economic evaluations typically ranged between 55 and 75 years, and expanding LDCT lung cancer screening to very old age groups may not be cost-effective as the additional health benefits are likely to be low and offset by considerable additional cost for screening, diagnostic testing and subsequent treatment. Screening starting age was also tested in sensitivity analyses and found to be an important determinant of intervention cost-effectiveness.

methods, components and factors to consider when assessing the cost of LDCT-screening for lung cancer

Basic cost-components for economic evaluations of LDCT-screening for lung cancer include screening cost, cost of diagnosis, treatment cost, supportive and continuing care cost and palliative care cost. Besides general methodological characteristics, such as the economic perspective, time horizon and discount rates, as well as methods and data for cost-assessment, relevant cost-factors considered in economic evaluations of lung cancer screening with LDCT include, amongst others, screening programme participation, LDCT-sensitivity and specificity, the effects of inconclusive indeterminant and incidental findings, the cost (and health effects) of screening, diagnostic and care-related complications, as well as length-bias, lead-time bias and potential over-diagnosis.

Discussion

methodological factors for evaluation of LDCT-screening in Austria including e.g.,

risk stratification

An economic evaluation for Austria should evaluate LDCT-screening for lung cancer against 'no screening' from a healthcare system perspective, compare different starting/stopping ages for screening and consider an assessment of different eligibility criteria (e.g. pack-years, time since smoking cessation, occupational risks). The use of validated risk assessment tools should be tested, and patient identification and recruitment should be based on experiences from existing screening programmes in Austria, thoroughly embedded within existing structures of healthcare provision, and reasonable assumptions should be made with respect to screening participation rates and related cost. The optimal interval and frequency of LDCT-screening for lung cancer should also be evaluated in an economic evaluation for Austria.

lifetime horizon (at least horizon of 25 years) recommended

The potential long-term impact of LDCT-screening on future cost and health benefits warrants a lifetime perspective for an Austrian model but because of the typical age-range of screen-eligible populations, a time horizon of at least 25 years should be considered. Based on Austrian guidelines for health economic evaluation, a discount rate of 5.0% for both cost and health benefits should be adapted for the base case, and for sensitivity analysis, a range of discount rates between 3.0% and 10.0% should be tested and reported.

discount rate at 5.0% for cost and effects

health outcomes assessed in terms of QALYs and LYS

health state utilities from the EQ-5D instrument

Estimates of clinical effectiveness should be based on a quantitative synthesis of the best available evidence from RCTs on lung cancer screening with LDCT as reviewed in Part I of this project. Health outcomes should generally be assessed in terms of quality-adjusted life-years (QALYs), but results should be reported both unweighted in terms of life-years saved (LYS) and weighted in terms of QALYs. Health state utilities should be based on the EuroQol-5D instrument, and in the absence of an Austrian value-set, estimates from another jurisdiction may be adopted (such as those available for Germany). Heterogeneity and uncertainty should be assessed through appropriate sensitivity and scenario analyses.

treatment cost, palliative care cost stratified by cancer stage

possible cost-factors, e.g., false-positives, false-negatives, over-diagnosis

Data for resource use should preferably be sourced from administrative databases which contain comprehensive information on inpatient and outpatient care for lung cancer treatment, and unit cost should be based on Austrian tariffs. If administrative data are not available, other data sources, such as data from published literature, should be considered. Because of the anticipated stage-shift though LDCT-screening, the cost for treatment, supportive and continuing care (and perhaps also end-of-life care) should be stratified by cancer stage of progression and time after surgery. Screening-test sensitivity and specificity should also be incorporated in an Austrian model as otherwise, the cost and health effects associated with false-positive and false-negative test results may remain unclear. Likewise, an Austrian model should consider the effect of inconclusive and indeterminant findings on both cost and health outcomes; screening, diagnostic and care-related complications; incidental findings; as well as length-bias, over-diagnosis, and lead-time bias.

adapting an existing model or a new model for Austria?

Before conducting an economic evaluation of LDCT-screening for lung cancer in Austria, however, a decision should be made as to whether to adapt an existing model or to build a de novo model for the Austrian context.

Conclusions

Lung cancer screening is a cost-intensive intervention

Lung cancer screening is a cost-intensive intervention, and introducing it on a population-level generally depends both on its cost-effectiveness and likely budget impact. A national rollout would therefore require sufficient willingness and ability to pay for the intervention, making lung cancer screening with LDCT generally more interesting in the context of higher performing and stronger funded healthcare systems.

no clear contentions about the cost-effectiveness of LDCT lung cancer screening possible

Given considerable variation in both study methodology and results, it is not possible to make contentions about the potential cost-effectiveness of LDCT-screening for lung cancer. Studies are not just characterised by different assumptions about screening eligibility, screening intervals and frequency, but also by different data, models, costing methods, and consideration of screening-specific drivers of intervention cost and outcomes that would potentially affect the cost-effectiveness of LDCT-screening. Further to that, studies under review also applied different cost-effectiveness thresholds to interpret findings, which further complicates making a reliable judgement about the cost-effectiveness of LCTD-screening for lung cancer in Austria.

Annual screening more effective but less cost-effective than biennial screening

Annual screening with LDCT may be more effective compared to longer screening intervals, but its additional cost make it less cost-effective. Annual screening would therefore have a stronger budget-impact and simultaneously require higher willingness to pay for a unit of health gain to be regarded cost-effective.

health economic evaluation for LDCT-screening needed for Austria

An economic evaluation for the Austrian context is therefore warranted, together with the assessment of the potential budget impact of LDCT-screening in Austria. Future research may also look into the development of an Austrian value set for the EQ-5D instrument as well as the estimation of a threshold value to determine intervention cost-effectiveness in the Austrian context.

1 Introduction

Lungenkrebs häufigste krebsbedingte Todesursache in Österreich (Ö)

Lung cancer belongs to the most common cancers in Europe (EU-27) and it is also the most frequent cancer-related cause of death in men and the second most frequent cancer-related cause of death in women, after breast cancer [1]. In Austria, lung cancer accounts for around 10.8% of all newly diagnosed cancers in women and 12.9% in men [1]. In terms of mortality, lung cancer is responsible for 16.6% of cancer-related deaths in women and 20.9% in men, making it the most frequent cancer-related cause of death in Austria [1].

Rauchen ist der wichtigste Risikofaktor für Lungenkrebs, aber auch Belastungen am Arbeitsplatz sowie bestimmte Vorerkrankungen können das Lungenkrebs-Risiko erhöhen

Most lung cancer cases are attributed to smoking, but occupational factors such as radon, asbestos or particulate matter exposure may also increase the risk for developing the disease. In addition, pre-existing diseases of the lung or bronchial systems, such as chronic obstructive pulmonary disease (COPD) or fibrosis increase lung cancer risk, but smoking remains the single most important risk factor, accounting for 90.0% of new cases in men and 80.0% in women [2]. Quantity and duration of smoking, as well as the time since smoking cessation further affect the risk of developing lung cancer. The age-specific incidence of the disease shows that lung cancer typically occurs at an older age, with the incidence increasing from the age of 40 onwards, and most people diagnosed with lung cancer being 65 or older [1]. More information on the health condition, its risk factors, the prevalence of lung cancer, current clinical practice and, most importantly, synthesis and analysis of the available clinical evidence on lung cancer screening in risk groups, is available from Part I of this project.[1]

verschiedene internationale Studien zeigen eine mögliche Reduktion in der Lungenkrebs-mortalität durch LDCT-Screening

In 2011, results from the National Lung Screening Trial (NLST) became available. This trial compared low dose computed tomography (LDCT) for lung cancer screening against screening with chest X-ray. Results from the NLST indicated a potential relative reduction in mortality from lung cancer through LDCT-screening of 20.0% [3]. In Europe, for instance, the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) assessed the potential mortality reduction from lung cancer through LDCT versus no screening, and also found a potential reduction in lung cancer mortality [4]. It should be noted at this point, however, that clinical studies on LDCT-screening for lung cancer were reviewed in Part I of this project, which found that there was evidence indicating a reduction in lung cancer mortality, though rated of low quality, as opposed to high-quality but non-significant results pointing towards little or no difference in overall mortality.[1] The authors, therefore, concluded that LDCT *may* reduce mortality compared with no screening.

LDCT-screening für Lungenkrebs in zahlreichen Leitlinien empfohlen

Since the publication of the abovementioned studies, numerous guidelines have recommended the use of LDCT-screening for lung cancer in high-risk individuals, such as those by the US Preventive Service Task Force (USPSTF), the European Society of Radiology (ESR) and the European Respiratory Society (ERS), amongst others.

[1] Available from: https://aihta.at/page/lungenkarzinomscreening-in-risikogruppen-systematische-review-s-zu-wirksamkeit-und-nutzen-teil-1-kosten-und-budgetfolgen-teil-2/en

Publikation verlässlicher Ergebnisse hinsichtlich des klinischen Nutzens von LDCT-Screening für eine ökonomische Evaluation notwendig

Until NLST results became available, several economic evaluations were already published, and Black et al. (2006) conducted a systematic review on the cost-effectiveness of LDCT-screening for lung cancer [5]. In their review, they concluded that many issues remain unresolved regarding the cost-effectiveness of the intervention and that more complete and transparent cost-effectiveness analyses are required. Also, clinical evidence should confirm that LDCT-screening for lung cancer does lead to a reduction in mortality, which is why the authors further concluded that, at the time, it was '*not currently possible to perform a rigorous analysis that could yield useful information to inform decision-making in this important area of public policy*' ([5] p.6).

Publikation neuer Studien zur Kosten-Effektivität von LDCT-Screening für Lungenkrebs → Update zur Kosten-Effektivität von LDCT-Screening notwendig

With the publication of results from the NLST, NELSON, and other trials (reviewed in Part I of this project), this situation presumably changed, and in the wake of this new evidence, several economic evaluations on LDCT-screening for lung cancer were published. This changed situation, however, requires a systematic assessment of the newly available evidence on the cost, effects, and cost-effectiveness of lung cancer screening with LDCT.

To support decision making concerning LDCT-screening programmes for lung cancer, and to inform the question of whether additional evidence on the cost-effectiveness of the intervention may be required, it was therefore decided to systematically review this body of literature, with a particular focus on the methods used to assess the cost of LDCT lung cancer screening so to inform a potential economic evaluation for the Austrian context.

2 Project aim and research questions

This report aims to systematically review the evidence on the cost-effectiveness, cost-utility and budget impact of lung cancer screening using LDCT versus no screening or screening with other imaging technologies (in particular chest-x-ray) in adult persons without confirmed or suspected lung cancer but at elevated risk. The three main objectives of this report are:

Projektziel: systematischer Review ökonomischer Evaluationen von Lungenkrebs-Screening-Programmen

- to obtain an overview of the methods that have been used in the included literature to estimate the cost of lung cancer screening;
- to systematically collect relevant cost-factors of lung cancer screening programmes that have been considered in published health economic evaluations; and
- to summarise economic evidence in terms of economic evaluations (cost-effectiveness and cost-utility) and budget impact.

The following three research questions result from the objectives:

3 Forschungsfragen:

Kostenparameter der Screening-Programme, Methoden der gesundheits-ökonomischen Studien, Studienergebnisse

1. Which methods have been used in the literature to estimate the cost of lung cancer screening including an interpretation of these methods and their likely impact on study results
2. What are the relevant cost-factors of lung cancer screening that have been considered in published health economic evaluations?
3. What are the results of existing economic evaluations of lung cancer screening in terms of cost-effectiveness and budget impact?

The clinical evidence of lung cancer screening does not form part of this systematic review as it falls within the scope of Part I of this project.[2] Neither does this report transfer or adapt published economic evaluation results to the Austrian context. Results of published studies are rather reported in their original currencies and their original cost year, though authors' conclusions based on comparison with locally applicable cost-effectiveness thresholds are thoroughly discussed.

klinische Effektivität & Übertragbarkeit der Studienergebnisse auf Ö nicht Ziel des Berichts

This should help Austrian decision-makers to obtain an overview of the relevant evidence as to whether lung cancer screening with LDCT may have, in principle, the potential to be cost-effective within the Austrian context. This report should also help to determine whether a de novo model to assess cost-effectiveness and/or budget impact of lung cancer screening with LDCT may be warranted for Austria, and if so, this review aims to provide methodological guidance for such an exercise, in particular concerning methods for appropriate cost-assessment of lung cancer screening programmes using LDCT.

Übersicht für österreichische Entscheidungsträger & methodische Hilfestellung für Durchführung einer gesundheits-ökonomischen Analyse

[2] Available from: https://aihta.at/page/lungenkarzinomscreening-in-risikogruppen-systematische-review-s-zu-wirksamkeit-und-nutzen-teil-1-kosten-und-budgetfolgen-teil-2/en

3 Methods

systematischer Review zur Kosten-Effektivität, Kosten-Nutzwert & Budgetfolgen von LDCT-Lungenkrebs-Screening

A systematic literature review of international studies reporting on the cost-effectiveness, cost-utility and/or budget impact of lung cancer screening using LDCT has been performed. In brief, the methods consisted of:

- a systematic search for peer-reviewed economic evaluations on lung cancer screening with LDCT in relevant publication databases, complemented with a thorough hand search for relevant references in key publications;
- extraction of data from includable studies based on a previously developed and pilot-tested data extraction form;
- tabulation of key methods used in available studies to estimate the cost of lung cancer screening with LDCT;
- tabulation of relevant cost-factors as reported in health economic evaluations of lung cancer screening using LDCT;
- tabulation of cost-effectiveness, cost-utility, and budget impact estimates from international studies as well as a brief discussion of results, without transferring them to the Austrian context;

Suchstrategie & Datenextraktion im Folgenden beschrieben

The search strategy as well as inclusion and exclusion criteria are detailed in Section 3.1 below. Section 3.2 reports on the methods for data extraction as well as qualitative and quantitative synthesis.

3.1 Systematic literature search

systematische Literatursuche & zusätzliche Handsuche

In brief, a database search strategy was developed based upon commonly used search terms for lung cancer screening and economic evaluations (see Section 3.1.1 and Appendix 8.5). The database search was complemented by a hand search of references from relevant publications. Inclusion and exclusion criteria were a priori defined and applied to the screening of titles and abstracts as well as the review of full-text papers (see Section 3.1.3).

3.1.1 Search strategy

systematische Literatursuche in 6 Datenbanken

A search in bibliographic databases was conducted to identify economic evaluations of lung cancer screening using LDCT published since 2005. The following bibliographic databases were searched:

- Medline via Ovid;
- Embase;
- Cochrane (CENTRAL);
- EconLit;
- the INAHTA-HTA-database; and
- the Centre for Reviews and Dissemination (CRD) databases (DARE, NHS-EED, HTA [archived content]).

Suchbegriffe vorab definiert. Vollständige Suchstrategie im Appendix

For each database, a search strategy was developed by an information scientist (TM). Search terms were defined a priori by the project team. A complete search strategy and results for each bibliographic database are reported in Appendix 8.5.

3.1.2 Selection of literature

verblindetes Abstract-Screening via Rayyan QCR

Volltext-Review unter 4-Augen-Prinzip

Database search results were imported to the software Rayyan QCRI [6] and two independent reviewers (CB and SW) screened titles and abstracts in a blinded fashion. After both reviewers concluded the process, results were compared, and conflicts were resolved by discussing the respective item. In case of doubt or remaining discrepancies, the respective paper proceeded further to the full-text review stage of this exercise. Full-text review and data- extraction were conducted by one researcher (CB) and a second researcher (SW) reviewed and confirmed results.

Reference lists of publications that were not excluded after screening titles and abstracts were also checked for additional relevant publications.

3.1.3 Inclusion and exclusion criteria

Ein- & Ausschlusskriterien

Study inclusion and exclusion criteria are based on the PICO defined in the study protocol in accordance with part I of this report[3] (Appendix 8.1 Table 8-1) and summarised in Table 3-1. They have been agreed upon by the project team before publications were screened.

Einschluss unterschiedlicher Formen von Lungenkrebs-Screening-Programmen mit LDCT in erwachsenen Personen ohne bestätigtem oder vermutetem Lungenkrebs jedoch mit erhöhtem Risiko

Studies were relevant for this systematic review if they assessed various forms of lung cancer screening programmes (systematic, opportunistic, different screening intervals, single or multiple screens, etc.) using either LDCT or LDCT + biomarkers in an adult population without confirmed or suspected cancer diagnosis but at elevated risk of lung cancer. Risk factors for the eligible screening population include previous or current smoking as well as occupational risks (such as radon, asbestos or fine particle exposure), COPD, or lung fibrosis. Lung cancer screening programmes using other diagnostic technologies than LDCT, LDCT as a second-line diagnostic or combined screening programmes for various conditions (including lung cancer) were not includable in this review. Studies assessing screening programmes combined with smoking cessation were only includable if a screening-only alternative was also reported and an incremental analysis was performed against a suitable comparator (either no screening or screening with other imaging technologies, in particular, chest x-ray).

[3] Available from: https://aihta.at/page/lungenkarzinomscreening-in-risikogruppen-systematische-review-s-zu-wirksamkeit-und-nutzen-teil-1-kosten-und-budgetfolgen-teil-2/en

Table 3-1: Inclusion and exclusion criteria for systematic literature review based on PICO-scheme

Criterion	Include	Exclude
Population	■ Adult persons (age 18 and older) without lung cancer (confirmed or suspected) at elevated risk of lung cancer ■ Risk factors: current or previous tobacco smoking, occupational toxins (e.g. radon, asbestos or fine particle exposure), COPD, lung fibrosis	■ Patients with confirmed or suspected cancer, including lung cancer ■ Persons under the age of 18
Intervention	■ Various forms of lung cancer screening, such as organised/systematic screening, opportunistic screening, screening at various intervals, single or multiple screen using either ■ Low-dose chest computer tomography (LDCT) or ■ LDCT + biomarkers	■ Screening with imaging technologies other than LDCT ■ Using LDCT as a second-line diagnostic ■ Using LDCT but not within the context of a formal lung cancer screening programme ■ Combined screening programmes, e.g. ■ Screening for various conditions, including lung cancer (such as whole-body LDCT) ■ Combined screening and smoking cessation programmes, unless incremental analysis includes a screening-only alternative
Comparator	■ No screening ■ Screening for lung cancer using other imaging technologies, in particular, chest x-ray	■ No comparator ■ Screening with non-imaging technologies
Study type	■ Cost-effectiveness analysis (CEA) ■ Cost-utility analysis (CUA) ■ Budget impact analysis (BIA)	■ Cost-analysis (CA) ■ Cost-minimisation analysis (CMA) ■ Cost-benefit analysis (CBA) ■ Financial analysis, return on investment analysis (ROI) or profitability analysis ■ Studies not reporting incremental analysis
Study methodology	■ Model-based studies ■ Trial-based studies	■ Systematic reviews of relevant studies ■ (though these will be identified through database searches and retained for hand searching relevant references)
Study perspective	■ Healthcare system ■ Public payer ■ Societal	■ Provider/hospital/commercial payer
Publication period	■ Studies published since 2005	■ Studies published before 2005
Publication type	■ Peer-reviewed journal articles ■ Health Technology Assessment (HTA)-reports	■ Editorials, notes, letters, opinions, discussions ■ Conference abstracts & oral presentations ■ Abstracts not linked to a full-text paper
Language	■ Studies published in English and German Language	■ Studies published in any other language

Abbreviations: BIA: budget impact analysis; CA: cost-analysis; CBA: cost-benefit-analysis; CEA: cost-effectiveness analysis; CMA: cost-minimisation analysis; COPD: chronic obstructive pulmonary disease; CUA: cost-utility-analysis; HTA: Health Technology Assessment; LDCT: low dose computed tomography; ROI: return on investment;

Einschluss von CEAs, CUAs & BIAs unter Berücksichtigung der Gesundheitssystem-perspektive, Zahlerperspektive oder gesellschaftlichen Perspektive

As this review aims to inform a potential economic evaluation of LDCT-screening for lung cancer in the Austrian setting, we deemed cost-effectiveness analyses (CEAs), cost-utility-analyses (CUAs) and budget impact analyses (BIAs) performed from either a healthcare system, public services or societal perspective as relevant for inclusion, whilst other study types (such as cost analyses (CA), financial return on investment (ROI) or profitability-analyses of LDCT-screening for lung cancer) were not included. Cost-minimisation analyses (CMA) and cost-benefit analyses (CBA) were excluded from further review,

as were studies reporting results from a provider, hospital or health maintenance organisation (HMO) perspective.

ökonomische Evaluationen entlang experimenteller Studien und modellbasierte Studien einschlussfähig

We considered both model and trial-based economic evaluations published as either peer-reviewed journal articles or HTA-reports as relevant for review, whilst systematic reviews of relevant studies were identified through database searches and retrieved for hand searching relevant references, but not included for data extraction. Editorials, notes, letters, opinion pieces and discussions were excluded from review, as were conference abstracts, oral presentations and abstracts not linked to full-text papers.

Studien vor 2005 vom Review ausgeschlossen

We also excluded studies published before 2005 as both screening technologies and the related clinical and economic evaluation evidence-base significantly evolved since then. Indeed, studies published before 2005 were previously reviewed by Black et al (2006), who concluded that, in light of the evidence existing until then, '*more complete and transparent cost-effectiveness analyses are required*' and that *'the introduction of a population screening programme should depend on confirmation that screening for lung cancer using CT does lead to a reduction in mortality* ([7], p. 38). Recent large-scale clinical studies (such as the NSLT [3]) seem to confirm this potential reduction in mortality from LDCT-screening for lung cancer, and these findings, in particular, have stipulated this systematic review.

Studienqualität wurde a priori nicht bewertet

Finally, an explicit assessment of study quality was not conducted to obtain a thorough overview of the methods that have been used in the literature to estimate the cost of lung cancer screening, including those examples that may be regarded of lower quality. However, inclusion and exclusion criteria specified in Table 3-1 ensured that at least some basic standards were met by studies includable for qualitative synthesis.

3.2 Data extraction and synthesis of evidence

Datenextraktion im 4-Augen-Prinzip

Full-text copies of all studies deemed relevant after screening titles and abstracts were obtained, together with respective supplements and appendices. The first reviewer (CB) assessed full-texts and tentatively decided upon inclusion or exclusion of the respective item. The second reviewer (SW) checked decisions of the first reviewer and any disagreements between reviewers were resolved through discussion until consensus was achieved.

3.2.1 Data extraction

Tabellen für Datenextraktion pilotiert & weiter angepasst

A data extraction form was developed and implemented in Microsoft Excel-based upon the aim and objectives of this report (see chapter 2). Previously published systematic reviews on the topic were also used to complement and refine the data extraction form [5, 8-11]. After piloting the form, a few amendments were agreed upon by the project team, and the final version was used to extract data from all includable studies. The first reviewer (CB) independently extracted data and the second reviewer (SW) checked the data extracted. Again, any disagreements between reviewers were resolved through discussion until consensus was achieved.

Appendix 8.2 (see Table 8-2) provides an overview of the items included in the final data extraction form, together with an explanation for each item. In brief, the data extraction form consisted of 71 items grouped in ten categories, namely:

- *General study characteristics*, such as study type, research question, study country and currency, timing and publication year, funding source(s) and author affiliations/conflict of interest;
- *Population characteristics and risk factors*, such as age group(s) and population risk factors, in particular, smoking history and occupational risks;
- *Intervention (screening) characteristics*, for instance, patient identification and enrolment into the screening programme, screening intervals and duration of the screening programme; as well as LDCT sensitivity and specificity;
- *Comparator characteristics*, in particular, the type of comparator (no screening, other screening technology or other screening programme specifications);
- *Outcome measurement*, so to specify how health outcomes were measured, together with the source of effectiveness data and the instrument to elicit health-related quality of life (HrQoL-)weights;
- *General methodological characteristics*, including the study perspective, time horizon and discount rates for costs and effects in the base case, the analytic approach, model type and source of clinical effectiveness data;
- *Specific costing methods*, such as costing methodology, data sources for resource use and unit cost, cost-items considered in the analysis, and several screening-specific cost-factors, including participation rate, administration, recruitment and overhead cost, cost of LDCT-screening and diagnosis, cost of lung cancer treatment, supportive and continuing care, cost of adverse events from screening, cost of over-diagnosis, inconclusive, false positive or false negative results, cost of (confirmation and/or treatment of) incidental findings, direct non-medical cost, indirect non-medical cost; as well as adjustment of lead-time bias and length-bias;
- *Results, conclusions, and limitations*, including estimates of incremental cost, incremental effects and incremental cost-effectiveness ratios (ICERS) or BIA results in the base case, cost-effectiveness-thresholds applied by authors to interpret findings, conclusions drawn and limitations stated by authors;
- *Sensitivity and scenario analysis*, so to record whether sensitivity analysis has been conducted and reported, the type of sensitivity analysis, main parameters and assumptions tested, together with main findings; and
- a final *comments*-section to record any additional study specifics that would warrant further discussion.

Datenextraktionstabelle umfasst 10 Kategorien mit insgesamt 71 Unterpunkten, z. B.:

Studiencharakteristika,

Charakteristika der Population,

Charakteristika der Intervention,

Charakteristika der Vergleichsintervention,

etc.

3.2.2 Qualitative synthesis

qualitative Synthese folgt den methodischen Richtlinien des Cochrane-Handbuchs

Following the recommendation from the Cochrane Handbook, we summarised economic evidence through tabulation of the characteristics and results of studies included in this systematic review [12]. The primary purpose for qualitative synthesis was to identify and understand key economic trade-offs and causal relationships relevant for the cost-effectiveness of lung cancer screening using LDCT and to identify and summarise methods for assessing the cost of lung cancer screening with LDCT as this information could lay the foundations for the development of a bespoke model for the Austrian context.

Fokus auf Costing-Methoden für Lungenkrebs-Screening-Programme

Therefore, we summarised the information extracted from includable studies in evidence tables and discussed study characteristics and results throughout this report. Special emphasis was placed on the methods for cost-assessment within economic evaluations and to discuss key determinants of lung cancer screening cost.

3.2.3 Quantitative synthesis

quantitative Synthese gesundheits-ökonomischer Daten nicht aussagekräftig, daher auch nicht Teil dieses Reviews

We also followed the recommendation from the Campbell and Cochrane Economics Methods Group, who argued that "*the purpose of producing economics components of Cochrane intervention reviews is not to identify a single precise estimate of incremental cost-effectiveness"* and that *"it is highly unlikely that such an estimate could be transferable and [...] the resultant pooled estimate is unlikely to be applicable in any setting.*" ([13], p.9). This has also been confirmed by Boehler (2012) and Boehler & Lord (2016), who conducted a multilevel meta-regression of incremental cost and effects of statins for the primary and secondary prevention of coronary artery disease and found that considerable variation in published cost-effectiveness estimates is due to variation in study methodology [14, 15]. Though their approach could help to identify the appropriate set of covariates for transferring cost-effectiveness information from one setting to another, they concluded that it would be premature to use their results *"to decide whether or not to transfer or adapt* [economic evaluation] *results to a particular context*" ([15],p 45).

gesundheits-ökonomische Ergebnisse tabuliert & im Hinblick auf die Studienziele analysiert

We, therefore, tabulated reported estimates of the incremental cost, cost-effectiveness and budget impact in original currencies, together with information on cost-effectiveness-thresholds applied by study authors to make contentions about the cost-effectiveness of lung cancer screening with LDCT in their respective settings. We also discussed these results in the light of contextual factors to inform the development of a bespoke model for the Austrian context.

3.3 Deviations from the study protocol

Abweichungen vom Studienprotokoll:

The methods of this review differ from the published study protocol[4] in two aspects:

Einschluss relevanter Studien auf CEAs, CUAs und BIAs begrenzt

- The yield of relevant studies led to a revision of inclusion and exclusion criteria for this systematic review. In particular, the project team decided to limit the inclusion of relevant studies to CEAs, CUAs and BIAs as these study designs are also those most relevant for the Austrian decision-maker. On the contrary, CMAs and CBAs or studies reporting results from a provider, hospital or HMO perspective were deemed excludable.

Update von bereits publizierten systematischen Reviews anstatt eines kompletten Reviews zu Studien ab 2005

- The number of relevant publications significantly increased in recent years and relevant papers published before 2017 were already systematically reviewed by other authors [5, 8-11]. The project team, therefore, decided to perform an update of published systematic reviews (in particular that of Snowsill et al., 2018 [11]) rather than a full review of studies published since 2005. Hence, results (with a focus on health economic methodologies) are reported for studies that met the abovementioned inclusion criteria but have not previously been included in systematic reviews on economic evaluations of lung cancer screening with LDCT, in particular the one performed by Snowsill et al. (2018) [11].

[4] Available from: https://aihta.at/page/lungenkarzinomscreening-in-risikogruppen-systematische-review-s-zu-wirksamkeit-und-nutzen-teil-1-kosten-und-budgetfolgen-teil-2/de

4 Results

This chapter summarises the results of the systematic review of studies on the cost-effectiveness, cost-utility and budget impact of lung cancer screening with LDCT. The following section 4.1 reports on the yield of information from both database search and hand searching references, general study characteristics, as well as population, intervention and comparator characteristics. General methodological factors, as well as a thorough review of costing methods applied in respective studies (research question 1), are reported in Section 4.2. Section 4.3 reviews the cost-factors considered in economic evaluations of lung cancer screening programmes with LDCT (research question 2). Section 4.4 reports on base-case results of included studies and findings from sensitivity and scenario analyses and puts these findings in context with study authors' contentions about the cost-effectiveness, cost-utility and budget impact of LDCT-screening for lung cancer (research question 3).

im Folgenden Methoden gesundheits-ökonomischer Studien, relevante Kostenfaktoren, sowie Ergebnisse der eingeschlossenen Studien dargestellt

4.1 Included studies

The yield of information from this systematic review is displayed in the PRISMA-flowchart in Figure 4-1. A total of 561 references were obtained by searching relevant publication databases, and after hand searching additional references, we obtained another six potentially relevant hits. The screening of 453 references after de-duplication led to the exclusion of 394 hits. Agreement between reviewers was high, with only 14 conflicts (3.1%) to resolve.

561 Ergebnisse durch Datenbankrecherche

453 Referenzen nach De-Duplizierung, davon 394 aus-geschlossen

The remaining 59 articles were reviewed in full text by the first reviewer (CB), and the second reviewer (SW) double-checked inclusion/exclusion decisions. 34 papers were excluded, of which three studies focused on patients with a confirmed cancer diagnosis. One further study was not lung cancer-specific but rather reviewed methods for budget impact analysis of cancer screening in general. 14 papers were excluded as their study design did not fall into the scope of this review exercise, i.e. cost-analysis (six studies); systematic reviews (three studies); wrong study perspective (two studies); no economic evaluation (two studies); financial return on investment analysis (one study). 13 conference abstracts and one commentary were further excluded from the review. Finally, two publications [16, 17] were excluded as they reported on the same study as already included papers [18, 19].

59 Referenzen im Volltext-Review

34 Referenzen nach Volltext-Review exkludiert

25 studies remained in the review as they met all inclusion criteria specified in Table 3-1 above. However, of the 25 studies, 12 were previously included in other reviews on the same topic (four systematic reviews: [7, 9-11] and one non-systematic review: [8]). In this context, the systematic review by Snowsill et al. (2018) [11] proved to be particularly relevant and similar in scope as compared to this report. From the remaining 13 studies, 12 were published in 2017 or later, which indicates a vast increase in relevant publications in recent years.

25 Studien erfüllen Einschlusskriterien

12 Studien bereits in früheren Reviews berücksichtigt

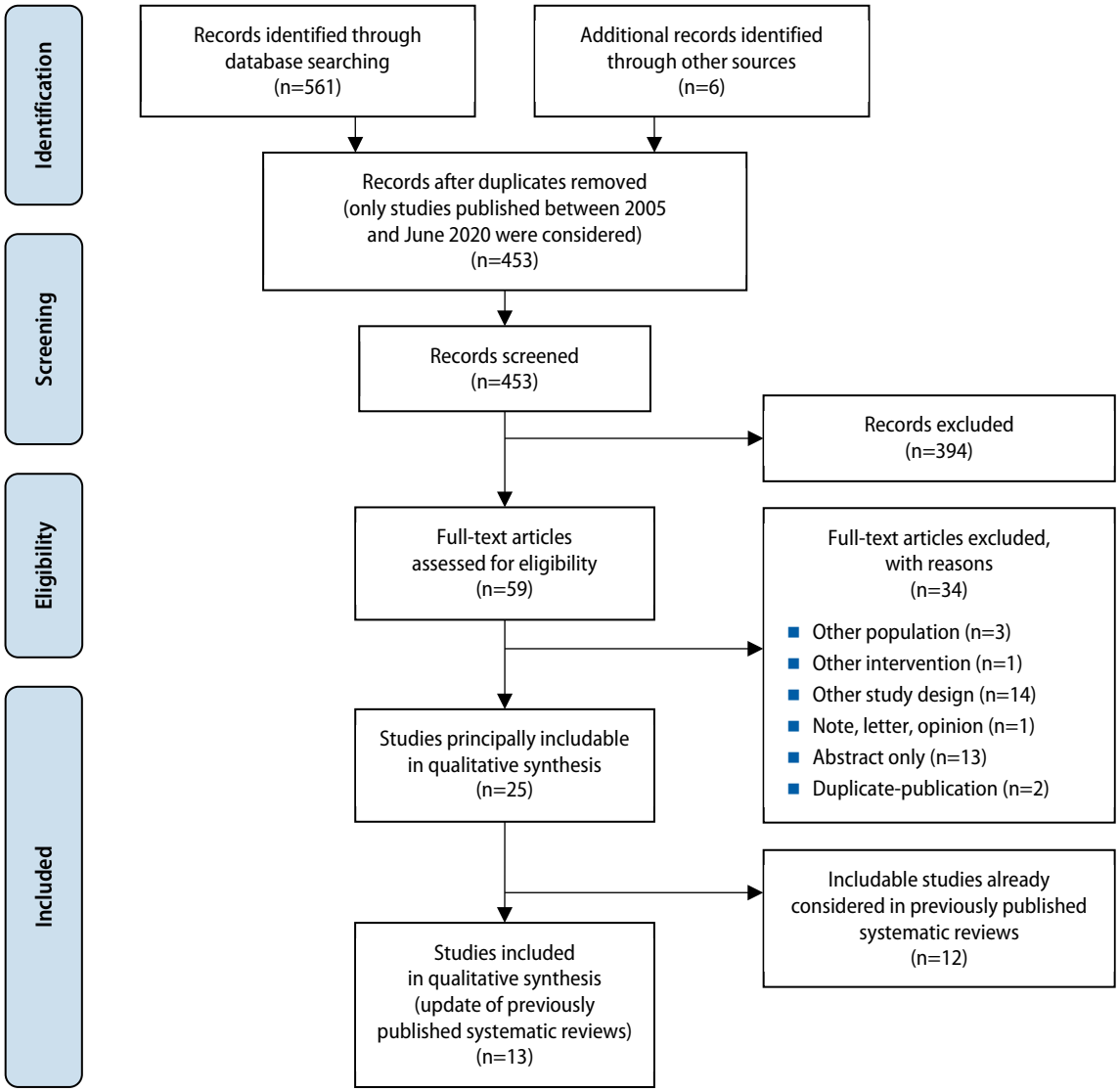

Figure 4-1: Display of the selection process (PRISMA Flow Diagram); Source: Own drawing adapted from [20]

13/25 Studien für qualitative Analyse eingeschlossen

Table 4-1 provides an overview of includable studies (n=25) and whether they were previously reviewed by other authors. Only studies that were not previously reviewed by others (in particular Snowsill et al. (2018) [11])were included for qualitative synthesis (n=13).

Table 4-1: Studies includable (n=25) and included (n=13) in qualitative synthesis

Citation	Previously reviewed in?					Study included in qualitative synthesis?
	Snowsill et al., 2018 [11]	Raymakers et al., 2016 [9]	Puggina et al., 2016 [10]	Goulart et al., 2012 [8]	Black et al., 2006 [5]	
Veronesi et al., 2020 [21]						Yes
Criss et al., 2019 [22]						Yes
Toumazis et al., 2019 [23]						Yes
Hinde et al., 2018 [24]						Yes
Hofer et al., 2018 [25]						Yes
Jaine et al., 2018 [26]						Yes
Kumar et al., 2018 [27]						Yes
Snowsill et al., 2018 [11]						Yes
Tomonaga et al., 2018 [28]						Yes
Wade et al., 2018 [29]						Yes
Cressman et al., 2017 [30]						Yes
Ten Haaf et al., 2017 [31]	X					
Yang et al., 2017 [32]						Yes
Field et al., 2016a & 2016b [16, 18]	X					
Goffin et al., 2016 [33]	X					
Goffin et al., 2015 [34]	X					
Black et al., 2014 & 2015 [17, 19]	X	X	X			
Tabata et al.,2014 [35]	X					
Guo, et al., 2014. [36]						Yes
Pyenson et al., 2014 [37]	X	X	X			
Shmueli et al., 2013 [38]	X	X	X			
Goulart et al., 2012 [8]	X					
McMahon et al., 2011 [39]	X	X	X	X		
Whynes., 2008 [40]	X					
Manser et al., 2005 [41]	X	X	X	X		

Anzahl relevanter Studien fast verdoppelt seit 2017

The cumulative distribution of includable publications and studies considered for qualitative synthesis is illustrated in Figure 4-2. As can be seen, the number of published studies vastly increased during the past three years. Indeed, 12 of 25 includable studies were published between 2017 and June 2020.

13 Studien zwischen 2005 und 2016 publiziert

The remaining 13 studies were published in the twelve years before, between 2005 and 2016. One study published in 2017 has already been reviewed by Snowsill et al. (2018) [11], whilst only one study [36] published in 2014 has not previously been included in a systematic review. This provides strong support for the project teams' decision to perform an update of the systematic review from Snowsill et al. (2018) [11], rather than a complete review of all 25 includable studies.

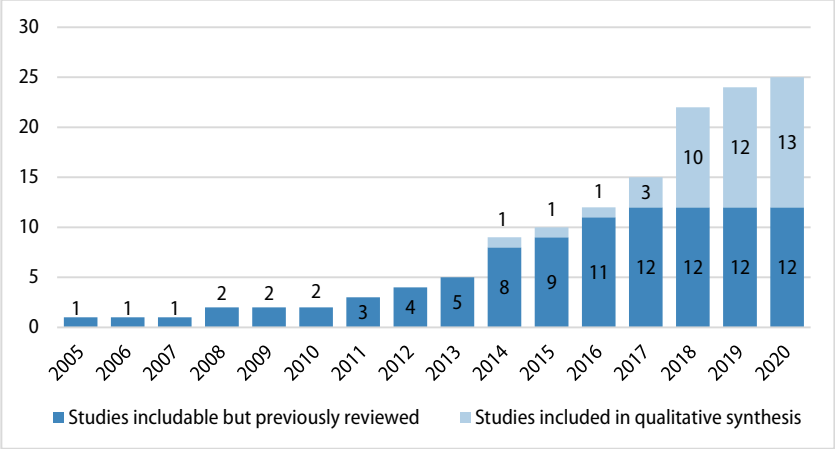

Figure 4-2: Cumulative distribution of includable and included studies by publication year; Source: own drawing

Table 4-2: Excluded studies previously included in other systematic reviews, with a reason for exclusion

Citation	Previously reviewed in?					Reason for exclusion
	Snowsill et al., 2018 [11]	Raymakers et al., 2016 [9]	Puggina et al., 2016 [10]	Goulart et al., 2012 [8]	Black et al., 2006 [5]	
Villanti et al., 2013 [42]	X	X	X			Study design
Pyenson et al., 2012 [43]	X	X				Study design
Castleberry et al., 2009 [44]				X		Study design
Chien et al., 2009 [45]				X		Publication type
Beinfeld et al., 2005 [46]		X				Intervention
Wisnivesky et al., 2003 [47]	X		X	X	X	Published before 2005
Mahadevia et al., 2003 [48]	X	X	X	X	X	Published before 2005
Chirikos et al., 2002 [49]	X			X	X	Published before 2005
Chirikos et al., 2003 [50]		X				Published before 2005
Marshall et al.,2001a [51]	X	X	X	X	X	Published before 2005
Marshall et al.,2001b [52]	X	X		X	X	Published before 2005
Okamoto et al., 2000 [53]		X		X	X	Published before 2005

12 Studien für qualitative Analyse ausgeschlossen, da bereits in früheren Reviews inkludiert

Table 4-2 lists publications excluded from qualitative synthesis, which were, however, previously included in other systematic reviews on economic evaluations of lung cancer screening with LDCT, together with reasons for exclusion. Of the twelve studies, seven were published before 2005 and therefore excluded. Three studies were excluded because of their study design, one study focused on whole-body CT scan, and one citation was only available as a conference abstract.

Übersicht zu ausgeschlossenen Studien im Appendix

Appendix 8.3 (see Table 8-3) lists all papers subject to full-text review, which were excluded from review, together with their respective reason for exclusion.

4.1.1 General study characteristics

11 Studien bewerten Kosten-Nutzwert, 7 Studien Kosten-Effektivität & 3 Studien Budgetfolgen von LDCT-Screening

Table 4-3 summarises the aim of included studies, study type and location, as well as price (cost) year, funding and the currency, in which results are reported.

Most studies assess the cost-effectiveness (seven studies) and/or the cost-utility (eleven studies) of LDCT-screening for lung cancer versus no screening and report results on a national level. Three studies [21, 25, 36] also provided budget impact estimates in addition to CEA or CUA results, and three studies [21, 24, 36] assessed the intervention on a sub-national level.

5 Studien aus den USA/Kanada, 5 europäische Studien & 3 Studien aus Asien oder Australien/Neuseeland

Geographic coverage of studies includes the USA and Canada (five studies), Australia and New Zealand (two studies), Asia (one study) and Europe (five studies). Of the five European studies, two [11, 24] were conducted in a UK-setting, and one [25] respectively in Germany, Italy [21], and Switzerland [28].

Ziele der inkludierten Studien

Several studies highlight specific questions relevant for an economic evaluation of lung cancer screening in their respective study aims. For instance, Yang et al. (2017) specifically aimed to assess the role of lead-time bias[5] for economic evaluations of lung cancer screening in their economic assessment [32]. Cressman et al. (2017) and Kumar et al. (2018) explicitly addressed the question of risk-targeted selection of screening participants [27], whilst Criss et al. (2019) compared the cost-effectiveness and cost-utility of different screening strategies based on NLST, Centres for Medicare & Medicaid Services (CMS) and USPSTF protocols [22]. Jaine et al. (2018) aimed to assess unrelated future medical cost in their CUA of biennial LDCT-screening among high-risk individuals in New Zealand [26]; whilst Toumazis et al. (2019) aimed to incorporate the Lung CT screening reporting and data system (RADS) guidelines to manage indeterminate findings [23]. The evaluation conducted by Hinde et al. (2018) gives special attention to patient recruitment into lung cancer screening programmes, particularly in '*hard-to-reach*' deprived communities, and in this context, they also assess the role of community-based lung health checks and mobile LDCT units [24].

[5] Lead-time bias refers to a situation when lung cancer patients are diagnosed earlier through LDCT-screening but their death occurs at the same time as it would have without screening. An earlier diagnosis may therefore extend the time between diagnosis and death, but not actual patient survival (Black et al., 2006 [5]. See also page 51).

Table 4-3: General characteristics of included studies

Citation	Aim of the study	Study type	Study country (province)	Currency	Timing (price year)	Funding
Guo et al.,2014 [36]	To assess the cost-effectiveness, cost-utility and budget impact of adopting lung cancer screening with LDCT in Alberta (Canada).	CUA BIA	Canada (Alberta)	CAD	2012	Public
Yang et al., 2017 [32]	To evaluate the cost-utility of implementing three annual LDCT-screenings for lung cancer in Taiwan with explicit consideration of lead-time bias and quality of life changes.	CUA	Taiwan	USD	2013	Public
Cressman et al., 2017 [30]	To assess the cost-utility of LDCT lung cancer screening for individuals based on an individual risk-score calculated from a risk prediction model compared to high-risk and low-risk unscreened populations	CUA	Canada	CAD	2015	NGO
Wade et al., 2018 [29]	To assess the cost-effectiveness and cost-utility of LDCT lung cancer screening among high-risk individuals in Australia, by applying Australian cost and survival data to the outcomes observed in the NLST trial	CEA CUA	Australia	AUD	2015	Not stated
Tomonaga et al., 2018 [28]	To assess the cost-effectiveness of LDCT lung cancer screening in a population-based setting in Switzerland and to compare different screening scenarios in terms of stop ages, eligibility criteria and screening intervals.	CEA	Switzerland	EUR	2015	NGO & public
Snowsill et al., 2018 [11]	To estimate the clinical effectiveness and cost-utility of LDCT lung cancer screening in high-risk populations, including a systematic review of cost-effectiveness and a de novo model for the UK setting.	CUA	UK	GBP	2016	Public
Kumar et al., 2018 [27]	To assess the cost-effectiveness and cost-utility of risk-targeted selection for lung cancer screening with LDCT compared with NLST eligibility criteria.	CEA CUA	USA	USD	2016	Public
Jaine et al., 2018 [26]	To assess the effects, costs (including unrelated future healthcare cost) and cost-utility of biennial LDCT-screening among high-risk individuals in New Zealand	CUA	New Zealand	USD	2011	Public
Hofer et al., 2018 [25]	To assess the cost-effectiveness and cost-utility of a population-based lung cancer LDCT-screening program for high-risk individuals from a German payer-perspective	CEA CUA (BIA)	Germany	EUR	2016	Industry
Hinde et al., 2018 [24]	To assess the cost-effectiveness and cost-utility of a community-based LDCT-screening pilot for lung cancer in Manchester (UK), with explicit consideration of recruitment of patients in 'hard-to-reach' deprived communities and addressing the role of community-based lung health checks and mobile LDCT units.	CEA CUA	UK (Manchester)	GBP	Not clearly stated, (presumably 2015)	Not stated
Toumazis et al., 2019 [23]	To assess and compare the cost-utility of 199 LDCT-screening strategies for lung cancer whilst incorporating the Lung-RADS guidelines to manage indeterminate findings for the US population.	CUA	USA	USD	2018	Public
Criss et al., 2019 [22]	To assess the cost, effectiveness, cost-effectiveness and cost-utility for three screening strategies versus no-screening based on the NLST, CMS, and USPSTF eligibility criteria from a US healthcare perspective.	CEA CUA	USA	USD	2018	Public
Veronesi et al., 2020 [21]	To assess the cost-effectiveness and cost-utility of LDCT-screening for lung cancer in high-risk individuals from an Italian tax-payer perspective.	CEA CUA BIA	Italy (Lombardy)	EUR	Not clearly stated, (presumably 2017)	Not stated

Notes: AUD: Australian dollar; BIA: budget impact analysis; CAD: Canadian dollar; CEA: cost-effectiveness analysis; CMS: Centers for Medicare & Medicaid Services; CUA: cost-utility analysis; EUR: Euro; GBP: Great Britain pounds; LDCT: low dose computed tomography; NGO: non-governmental organisation, NLST: National Lung Screening Trial; RADS: Lung CT screening reporting and data system; UK: United Kingdom; USA: United States of Amerika; USD: United States dollar; USPSTF: U.S. Preventive Services Task Force.

Figure 4-3 displays the distribution of studies according to their respective price (cost) year. Most of the 13 included studies report results in 2015 or 2016 cost/prices. As noted, however, this information is not entirely clear for two of the included studies [21, 24].

Großteil der Studien reportiert Kosten & Ergebnisse für 2015/2016

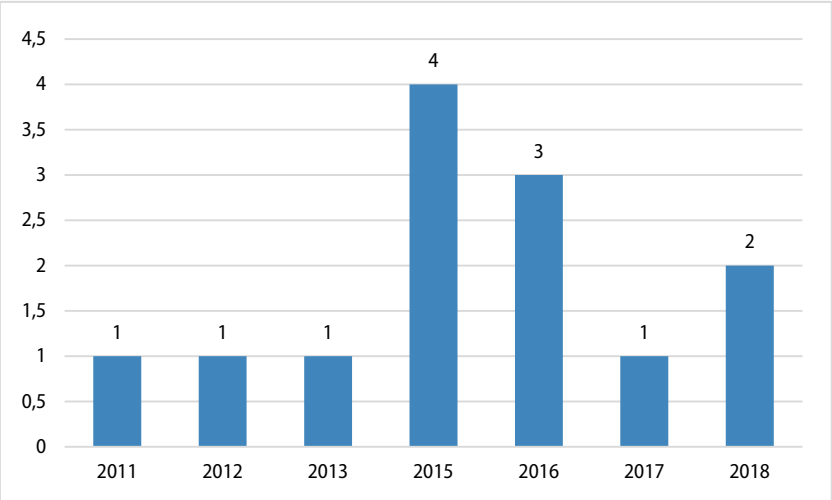

Figure 4-3: Timing of included studies (price/cost year); Source: own drawing

Finally, more than half of the studies included were publicly funded (seven studies); whilst one study [28] was funded both by NGOs and the public; one study [30] was funded by NGOs; one study [25] received industry funding. Funding was unclear for three studies [21, 24, 29].

7/13 Studien öffentlich finanziert

4.1.2 Population, intervention and comparator characteristics

Table 4-4 summarises eligibility criteria for lung cancer screening as defined by the studies included for qualitative synthesis.

Zulassungskriterien für Lungenkrebs-Screening

In terms of starting/stopping ages for screening, most studies defined screening-eligible populations between 55 and 74 or 75 years (7 studies). However, several studies tested different screening-protocols by altering starting/stopping ages for screening-eligible populations. For instance, Tomonaga et al. (2018) assessed screening scenarios for populations between 50, 55 and 60 years (starting age) and 75, 80 and 85 years (stopping age), respectively [28]. Snowsill et al. (2018) and Toumazis et al. (2019) took a similar approach, though with different starting/stopping ages [23] , whilst Criss et al. (2019) specifically compared the NLST, CMS and USPSTF eligibility criteria for screening [22].

berechtigte Personengruppen für LDCT-Screening meist 55-75 Jahre alt

Table 4-4: Characteristics of screening eligible populations

Citation	Eligible age group(s)	Population risk factors
Guo et al.,2014 [36]	■ 55 to 75 years	■ ≥30 pack-years of smoking
Yang et al., 2017 [32]	■ 55 to 75 years	■ ≥30 pack-years of smoking
Cressman et al., 2017 [30]	■ 60 years (average age of enrollment) ■ Enrollment based on individual risk-scores	■ High-risk individuals ■ Enrollment based on individual risk-scores
Wade et al., 2018 [29]	■ 55 to 74 years	■ ≥30 pack-years of smoking and/or ■ ≤15 years since quitting
Tomonaga et al., 2018 [28]	■ Starting ages: 50, 55 and 60 years* ■ Stopping ages: 75, 80 and 85 years*	■ 10 to 40 pack-years of smoking* ■ Eligibility criteria based on NLST or NELSON
Snowsill et al., 2018 [11]	■ Starting ages: 55 and 60 years* ■ Stopping ages: 75 and 80 years*	■ Current or former smokers with a predicted lung cancer risk of 3,0%, 4,0% and 5,0%*
Kumar et al., 2018 [27]	■ 55 to 74 years	■ ≥30 pack-years of smoking and/or ■ ≤15 years since quitting
Jaine et al., 2018 [26]	■ 55 to 74 years	■ ≥30 pack-years of smoking and/or ■ ≤15 years since quitting
Hofer et al., 2018 [25]	■ 55 to 75 years	■ Heavy former and current smokers ■ (≥20 cigarettes per day)
Hinde et al., 2018 [24]	■ 55 to 74 years	■ Initial invitation to 'ever smokers' for risk assessment with $PLCO_{m2012}$ ■ LDCT-screening if 6 year LC risk ≥1.51%,
Toumazis et al., 2019 [23]	■ Starting ages: 55, 55, 60 and 65 years* ■ Stopping ages: 70, 75 and 80 years*	■ ≥20, 30, and 40 packyears and/or* ■ ≤10, 15, and 20 years since quitting*
Criss et al., 2019 [22]	■ Starting age: 55 years ■ Stopping ages: 74, 77 and 80 years* ■ Eligibility based on NLST, CMS, USPSTF	■ ≥30 pack-years of smoking ■ ≤15 years since quitting. ■ Eligibility based on NLST, CMS, USPSTF
Veronesi et al., 2020 [21]	■ 55 to 79 years	■ ≥30 pack-years of smoking ■ ≤15 years since quitting

*Notes: * Depending on the screening scenario. Abbreviations: CMS: Centers for Medicare & Medicaid Services; NELSON: Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST: National Lung Screening Trial; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer trial; USPSTF: U.S. Preventive Services Task Force*

Algorithmen zur Berechnung der individuellen Risiko-Scores

Cressman et al. (2017) took a different approach as they assess patient enrolment based on individual risk scores, estimated from the Prostate, Lung, Colorectal, and Ovarian Cancer trial ($PLCO_{m2009}$) risk prediction tool [30], developed within the PLCO-trial [54]. Their average age of enrolment is 60 years (Table 4-4). Finally, Veronesi et al. (2020) also defined screen-eligible populations from the age of 55, but extent eligibility criteria to 79 years of age [21].

Raucherstatus wichtigster Risikofaktor

In terms of population risk-factors, all studies focused on smoking history, and most of them defined eligibility of patients with at least 30 pack-years of smoking (seven studies) and/or a maximum of 15 years since quitting (five studies). Again, Tomonaga et al. (2018) and Toumazis et al. (2019) tested different eligibility criteria by altering the minimum number of pack-years (between 20 and 40 years) and the years since smoking cessation (between 10 and 20 years) [23, 28]. Snowsill et al. (2018) considered patient subgroups with a predicted minimum lung cancer risk of 3.0%, 4.0% and 5.0% respectively, based upon a purposely developed risk-prediction model with coefficients for baseline characteristics age, sex and smoking status [11]. Likewise, the $PLCO_{m2009}$ risk prediction tool used by Cressman et al. (2017) [30] includes predictors such as age, education, smoking history, coexisting COPD, family history of lung cancer, and body mass index (BMI) [55]. Finally, Hofer et al.

einige Studien nutzen Algorithmen zur Risikobewertung

(2018) defined screen-eligible patients as heavy current and former smokers with at least 20 cigarettes per day [25], whilst Hinde et al. (2018) regarded 'ever smokers' as eligible for an initial lung health check (LHC) [24], where six-year lung cancer risk has then been assessed using the $PLCO_{m2012}$ [55]. Those with a six-year lung cancer risk of ≥1.51% were eligible for LDCT-screening [24].

in einigen Studien keine Methoden (und damit Kosten) der Patient*innenidentifikation und -rekrutierung für LDCT-Screening spezifiziert

Table 4-5 summarises intervention and comparator characteristics of included studies. Patient identification and enrolment are important cost-components of lung cancer screening, in particular as screening participation rates of invited individuals are likely to be considerably below 100.0%. However, six of the 13 included studies did not specify the means of patient identification and enrolment for lung cancer screening. Two studies [27, 30] focused on the cost-effectiveness of risk stratification tools to identify eligible individuals, however, means of actual patient enrolment into the screening programme remain unclear. Guo et al. (2014) based patient identification and enrolment on physician recruitment [36], whilst Snowsill et al. (2018) assumed screening of primary care records for patient identification and subsequent patient recruitment through invitations sent from primary care units [11]. Hinde et al. (2018) identified patients who met eligibility criteria from participating general practitioner (GP) practices, and those eligible were subsequently invited to have a lung health check at a convenient community venue [24]. Individuals with a six-year lung cancer risk of ≥1.51%, $PLCO_{M2012}$ [54] were offered LDCT-screening, consisting of two annual screens including an immediate scan in a nearby mobile CT-scanner. Finally, Tomonaga et al. (2018) assumed cost for a centralised invitation of all eligible patients [28], and Jaine et al. (2018) included cost for screening administration to identify and invite eligible individuals [26].

unterschiedliche Screening-Intervalle und -Frequenzen zwischen analysierten Studien

Intervention protocols also vary considerably across studies in terms of screening intervals (Table 4-5), which is likely to impact both on cost and cost-effectiveness of lung cancer screening with LDCT. Two studies [22, 30] only assess annual LDCT-screening for lung cancer. Hinde et al. (2018) considered two consecutive annual screens [24], three studies [27, 29, 32] assessed three consecutive annual screens, and Veronesi et al. (2020) evaluated five consecutive annual screens [21]. However, in case of the study by Veronesi et al. (2020), it needs to be mentioned that the time horizon of their model is also limited to five years only [21] (see also Table 4-6.). Jaine et al. (2018) assessed a screening protocol with biennial LDCT-screens [26], whilst the remaining five studies tested alternative screening protocols with annual and biennial screening [23, 25, 36]; annual, biennial and triennial screening [28] and single-screening, triple annual screening and annually repeated screen scenarios, respectively [11].

am häufigsten verwendeter Komparator: „kein Screening"

Finally, as shown in Table 4-5, all but one study [27] compared LDCT-screening for lung cancer against a no-screening alternative. In this study, the authors compare LDCT-screening against chest-radiography based on NLST data. However, the authors rightly pointed out that their choice of the comparator may have biased results towards the study intervention, especially as previous evidence showed that chest-radiography may not effectively reduce lung cancer mortality [27].

Table 4-5: Intervention and comparator characteristics

Citation	Patient identification & enrollment for LDCT- screening	LDCT-Screening interval(s)	Comparator
Guo et al., 2014 [36]	■ Physician recruitment	■ Annual* ■ Biennial*	No screening
Yang et al., 2017 [32]	■ Not specified	■ Three consecutive annual LDCT-screenings	No screening
Cressman et al., 2017 [30]	■ High-risk individuals from NLST retrospectively identified with a risk prediction tool developed from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial ■ Patient identification and enrollment not further specified	■ Annual	No screening
Wade et al., 2018 [29]	■ Not specified	■ Three consecutive annual LDCT-screenings	No screening
Tomonaga et al., 2018 [28]	■ Centralised invitation of all eligible patients	■ Annual* ■ Biennial* ■ Triennal*	No screening
Snowsill et al., 2018 [11]	■ Identification of high-risk individuals from primary care records ■ Initial invitations sent from primary care units	■ Single screen* ■ Tripple screen (three consecutive annual screens)* ■ Annually repeated screen*	No screening
Kumar et al., 2018 [27]	■ Risk targeted screening ■ Patient identification and enrollment not further specified	■ Three consecutive annual LDCT-screenings	Screening with chest-radiography
Jaine et al., 2018 [26]	■ Cost for screening administration to identify individuals in the target population and cost for the actual invitation included	■ Biennial	No screening
Hofer et al., 2018 [25]	■ Not specified	■ Annual* ■ Biennial*	No screening
Hinde et al., 2018 [24]	■ Ever smokers aged 55–74 registered to participate GP practices were invited to have an LHC at convenient community venues ■ Those found to have a 6-year lung cancer risk of ≥1.51% were eligible for and offered LDCT-screening. ■ Immediate scan in a co-located mobile CT scanner	■ Two consecutive annual LDCT-screenings	No screening
Toumazis et al., 2019 [23]	■ Not specified	■ Annual* ■ Biennial*	No screening
Criss et al., 2019 [22]	■ Not specified	■ Annual	No screening
Veronesi et al., 2020 [21]	■ Not specified	■ Five consecutive annual LDCT-screenings	No screening

*Notes: * Depending on the screening scenario. Abbreviations: LDCT: low dose computed tomography; LHC; lung health check; NLST: National Lung Screening Trial.*

4.2 Methods of economic evaluations on LDCT-screening programmes for lung cancer

Methoden zur Schätzung der Kosten eines Lungenkrebs-Screening-Programms

This chapter is concerned with both general methodological characteristics of included studies (which may also impact on intervention cost and cost-effectiveness) as well as specific costing methods that have been used in the literature and how they are likely to impact on study results (research question 1). In order to address these issues, the chapter is organised in two main sections. Section 4.2.1 addresses general methodological characteristics of studies included for qualitative synthesis, whilst Section 4.2.2 focusses more concretely on costing methodology.

4.2.1 General methodological characteristics

Studienmethoden Effekt auf inkrementelle Kosten

The reason to include general methodological characteristics in this review, which is primarily concerned with costing of LDCT-screening for lung cancer, is that they too determine the incremental cost, effects and cost-effectiveness of included studies.

Gesundheitssystem-perspektive vs. Zahlerperspektive vs. gesellschaftliche Perspektive

For instance, the perspective chosen for economic assessment determines the cost to be considered for evaluation. A healthcare system perspective generally includes all direct medical cost, i.e. the cost that arise from the transaction of medical services, which are borne by the (public) healthcare system. A public service perspective goes further in that regard, as it also includes the cost to other public sectors, such as social services. A societal perspective mandates inclusion of not just direct medical cost, but also direct and indirect non-medical cost, such as out-of-pocket payments, transport cost, or work-loss (e.g., [56]).

lebenslanger Zeithorizont empfohlen → Diskontierung der Kosten & Effekte notwendig

Likewise, the time horizon of an economic evaluation determines the inclusion of future cost and effects of both, the technology under assessment and the respective comparator. A lifetime horizon is generally recommended when differences between intervention and comparator cost and effects are likely to last long into the future. This also means that, if an evaluation does not sufficiently extrapolate into the future, it may misrepresent both incremental cost and effects of the intervention under study (e.g. [56]). A related issue is that of discounting future cost and health benefits to respective net present values (NPVs). Higher discount rates lead to lower net present values and vice versa, and there is a long-standing debate over the use of differential discount rates for cost and health benefits, and the circumstances under which this may be justified (e.g. [57])

Studien wählen zumeist eine Gesundheitssystem-Perspektive

Table 4-6 summarises included studies with respect to their perspective, time horizon and discount rates for future cost and health benefits. Eight out of the 13 included studies apply a healthcare perspective, whilst two studies conducted in a UK-setting follow the recommendations of the National Institute for Health and Care Excellence [58] and apply a National Health Service (NHS) and Personal Social Services (PSS) perspective [11, 24]. Yang et al. (2017) and Cressman et al. (2017) adopted a public payer perspective [30, 32], and Veronesi et al. (2020) referred to an 'Italian taxpayer perspective' [21], though it needs to be mentioned that in all three studies, the cost considered are most closely linked to a healthcare system perspective. In addition to that, Cressman et al. (2017) were the only authors who also assessed LDCT-screening for lung cancer from a societal perspective through the inclusion of travel cost, productivity loss and caregiver cost [30] (see also Section 4.3).

1/13 Studien inkludierte gesellschaftliche Kosten, wie z. B. Transportkosten, Arbeitsausfall, etc.

Table 4-6: Reported perspective, time horizon and discount rates

Citation	Perspective reported	Time horizon	Discount rate	
			Cost	Benefits
Guo et al.,2014 [36]	■ Healthcare system	■ CUA: 25 years ■ BIA: 20 years	3.0%	3.0%
Yang et al., 2017 [32]	■ Public payer	■ Lifetime	3.0%	3.0%
Cressman et al., 2017 [30]	■ Public payer ■ Societal	■ Lifetime (30 years)	3.0%	3.0%
Wade et al., 2018 [29]	■ Healthcare system	■ 10 years ■ Lifetime	5.0%	5.0%
Tomonaga et al., 2018 [28]	■ Healthcare system	■ Lifetime	3.0%	3.0%
Snowsill et al., 2018 [11]	■ Healthcare system (NHS and PSS)	■ Lifetime	3.5%	3.5%
Kumar et al., 2018 [27]	■ Healthcare system	■ Lifetime	3.0%	3.0%
Jaine et al., 2018 [26]	■ Healthcare system	■ Lifetime	3.0%	3.0%
Hofer et al., 2018 [25]	■ Healthcare system	■ 15 years	3.0%	3.0%
Hinde et al., 2018 [24]	■ Healthcare system (NHS and PSS)	■ unclear/not stated	3.5%	3.5%
Toumazis et al., 2019 [23]	■ Healthcare system	■ Lifetime	3.0%	3.0%
Criss et al., 2019 [22]	■ Healthcare system	■ Lifetime (45 years)	3.0%	3.0%
Veronesi et al., 2020 [21]	■ "Taxpayer" (healthcare)	■ 5 years	3.0%	Unclear

Notes: NHS: National Health Service; PSS: Personal Social Services.

Studien adaptieren zumeist einen lebenslangen Zeithorizont

In terms of time horizon, six studies modelled the cost and health benefits of LDCT-screening for lung cancer over a lifetime horizon. Criss et al. (2019) chose a time horizon of 45 years [22], whilst Cressman et al. (2017) modelled the cost and health outcomes of LDCT-screening for lung cancer over 30 years [30]. Guo et al. (2014) modelled a 25 years horizon [36], Hofer et al. (2018) applied a 15-year time horizon [25], whilst Wade et al. (2018) compared a 10-year horizon with a lifetime horizon for assessing the cost and health benefits of LDCT-screening for lung cancer [29]. Veronesi et al. (2020) modelled a five-years time-horizon [21], and the time horizon modelled by Hinde et al. (2018) remains unclear [24].

Studien diskontierten Effekte & Kosten zumeist mit einem identischen Diskontsatz von 3,0%

Finally, there is a clear agreement between the 13 included studies in terms of the discount rates applied to cost and health benefits. All but one study adopted identical discount rates to cost and health benefits. Only Veronesi et al. (2020) discounted cost with 3.0%, whilst there appears to be no discounting of health benefits [21]. This reduced the net present value of the incremental cost of LDCT-screening for lung cancer, whilst health benefits remained unchanged, consequently leading to more favourable cost-effectiveness estimates of the intervention under study. Besides, all but three studies applied a 3.0% discount rate. The two studies [11, 24] conducted in the UK followed the NICE reference case [58] and applied a 3.5% discount rate to both cost and health benefits, whilst Wade et al. (2018) applied a 5.0% discount rate to both cost and health benefits [29].

analytischer Ansatz: Studienmethode & Modelltyp

Another aspect concerning the general methodological characteristics of health economic evaluations, namely the analytical approach comprising study method and model type, is briefly summarised in Table 4-7. A detailed assessment of the modelling methods, however, goes beyond the scope of this review.

inkludierten Studien beruhen auf unterschiedlichen modellbasierten Evaluationen

In brief, all 13 studies under assessment rely on some sort of modelling for assessing the incremental cost and health outcomes of LDCT lung cancer screening programmes, but their respective modelling methods differ: Three studies [24, 29, 32] adapted a lifetable approach. Two studies [25, 30] developed a Markov model to simulate patient transitions between lung cancer-related health states over their respective study time horizons and to weigh health states with respective cost and health benefits. One study [21] used a decision tree, and Snowsill et al. (2018) combined a decision tree with an individual patient simulation model within a discrete event simulation framework [11]. Kumar et al. (2018) relied on a multistate regression model [27]. Whilst Jaine et al. (2018) developed a macrosimulation stage shift model [26], all other studies relied on some form of microsimulation.

Table 4-7: Analytic approach

Citation	Study method	Model type	Model acronym
Guo et al.,2014 [36]	■ Model	■ Microsimulation	■ CRMM
Yang et al., 2017 [32]	■ Model	■ Life table	--
Cressman et al., 2017 [30]	■ Model	■ Markov model	--
Wade et al., 2018 [29]	■ Model	■ Life table	--
Tomonaga et al., 2018 [28]	■ Model	■ Microsimulation	■ MISCAN
Snowsill et al., 2018 [11]	■ Model	■ Discrete event simulation model & decision tree	--
Kumar et al., 2018 [27]	■ Model	■ Multistate regression model	--
Jaine et al., 2018 [26]	■ Model	■ Macrosimulation stage shift model	--
Hofer et al., 2018 [25]	■ Model	■ Markov model	--
Hinde et al., 2018 [24]	■ Model	■ Life table	■ UKLS model
Toumazis et al., 2019 [23]	■ Model	■ Microsimulation	--
Criss et al., 2019 [22]	■ Model	■ Microsimulation	CISNET
Veronesi et al., 2020 [21]	■ Model	■ Decision model, decision tree	■ --

Abbreviations: CISNET: Cancer Intervention and Surveillance Modelling Network; CRMM: Canadian Cancer Risk Management Model; MISCAN: MIcrosimulation SCreening Analysis; UKLS: UK Lung Cancer Screening Trial.

Großteil der inkludierten Studien beruhen auf Ergebnissen der NLST-Studie

Table 4-8 summarises general study methods with respect to sources for clinical effectiveness data and measures of health outcomes. As this exercise represents an update of a previous review of economic evaluations LDCT-screening for lung cancer [11], all but one study were published in 2017 or later. As a consequence, six of the studies included exclusively rely on the NLST as the source for clinical effectiveness estimates, which demonstrated a mortality benefit of LDCT-screening for lung cancer [3]. Another five studies combined or compared NLST-data with other sources of clinical effectiveness data, including NLST + PLCO [22, 23, 28], NLST + UK Lung Cancer Screening Trial (UKLS) [11], or NLST plus Continuing Observation of Smoking Subjects (COSMOS) [21]. Only two studies did not rely on any inputs from the NLST-trial: Hofer et al. (2018) [25] sourced clinical effectiveness data from the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), and Hinde et al. (2018) relied on primary data collection from their pilot study on community-based LDCT-screening for lung cancer in Manchester, UK [24].

Table 4-8: Clinical effectiveness and outcome measurement

Citation	The primary source of clinical effectiveness data	Measurement of health outcomes	HrQoL instrument (if applicable)
Guo et al.,2014 [36]	■ NLST	■ QALYs	■ Not clear/stated
Yang et al., 2017 [32]	■ NLST	■ QALYs	■ EQ-5D-5L
Cressman et al., 2017 [30]	■ NLST	■ QALYs	■ EQ-5D-3L
Wade et al., 2018 [29]	■ NLST	■ LYG ■ QALYs	■ SF-36
Tomonaga et al., 2018 [28]	■ NLST ■ PLCO	■ LYG	■ Not clear/stated
Snowsill et al., 2018 [11]	■ UKLS ■ NLST	■ QALYs	■ EQ-5D
Kumar et al., 2018 [27]	■ NLST	■ LYG ■ QALYs	■ Not clear/stated
Jaine et al., 2018 [26]	■ NLST	■ DALYs	■ Disability weights
Hofer et al., 2018 [25]	■ NELSON	■ LYG ■ QALYs	■ Not clear/stated
Hinde et al., 2018 [24]	■ Primary data collection	■ LYG ■ QALYs	■ EQ-5D
Toumazis et al., 2019 [23]	■ NLST ■ PLCO	■ QALYs	■ Not clear/stated
Criss et al., 2019 [22]	■ NLST ■ PLCO	■ LYG ■ QALYs	■ Not clear/stated
Veronesi et al., 2020 [21]	■ NLST ■ COSMOS	■ LYG ■ QALYs	■ Not clear/stated

Abbreviations: COSMOS: Continuing Observation of Smoking Subjects.; DALY: Disability-adjusted life years; EQ-5D: EuroQol 5 Dimensions; LYG: Life years gained; NELSON: Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST: National Lung Screening Trial; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer trial; QALY: Quality-adjusted life-years; SF-36: Short Form 36; UKLS: UK Lung Cancer Screening Trial;

klinische Effektivität & Sicherheit von LDCT-screening in Teil I dieses Projekts

The appraisal of the abovementioned sources for clinical effectiveness estimates constitutes an integral component of the clinical review of LDCT-screening for lung cancer conducted as Part I of this project. For a discussion of clinical studies, their methods, results, and strengths and weaknesses, we, therefore, refer to Part I of this project. [6]

Outcomes überwiegend in qualitätsadjusiterten Lebensjahren (QALYs) bewertet

Though it is not the focus of this review, Table 4-8 also briefly summarises measures of effectiveness and, if applicable, sources of health state utilities. All but one study measured health outcomes in terms of quality-adjusted life-years (QALYs, five studies), life-years gained (LYG, one study) or both (six studies). One study weighs lung cancer health states with disability weights, hence measuring health outcomes in terms of disability-adjusted life years (DALYs, [26]).

Nutzen überwiegend mithilfe des EQ-5D-Instruments ermittelt

Finally, the instrument to estimate health state utilities has been specified in six studies, with the EQ-5D (either in its 3-level or 5-level version) to be the most common choice. One study [29] used SF-36 values, and another study [26] applied disability weights.

[6] Available from: https://aihta.at/page/lungenkarzinomscreening-in-risikogruppen-systematische-review-s-zu-wirksamkeit-und-nutzen-teil-1-kosten-und-budgetfolgen-teil-2/en

4.2.2 Costing methods

This section provides a review of the methods and data sources used to estimate the cost of LDCT-lung cancer screening programmes as applied in the studies under review.

Methoden und Datenquellen zur Kostenerhebung

Methodology

Methods for cost assessment of LDCT-screening for lung cancer differ considerably between the studies under review. However, there are also a few principles for the cost-assessment of LDCT lung cancer screening that seem to hold across studies.

unterschiedliche Methoden bzgl. den Kosten

For instance, whilst the level of detail (i.e., micro- versus macro-costing approach) certainly varies between studies (and probably also within studies according to the respective cost-component of the patient pathway), there seem to be general 'blocks' of LDCT-lung cancer screening and treatment cost that most studies consider (Table 4-9).

z. B. Mikro- vs. Makro-Costing

Screening cost are typically assessed on a per-procedure level and assigned to each person recruited into the screening programme. Guo et al. (2014), for instance, included cost for physician recruitment, the screening test consultation (LDCT-screen), screening test interpretation, communication cost for the screen-result, and a consultation fee for test-positive patients [36]. Snowsill et al. (2018) included the cost of an initial invite and questionnaire, cost of scoring the questionnaire and risk stratification, cost of a follow-up letter, as well as cost of the actual LDCT-scan and a GP-consultation that leads to lung cancer referral [11]. Hinde et al. (2018) included screening cost for recruitment (invitation letters), lung health checks (including lung cancer risk assessment), an initial LDCT-scan and reporting immediately after the lung health check, as well as an LDCT-scan and reporting cost for a separate screening appointment [24].

Screening-Kosten meistens pro Durchführung und pro Screening-Teilnehmer*in

Other studies take a more aggregate approach for costing the screening component of the lifetime lung cancer patient pathway. In this context, it needs to be noted that some cost associated with screening also depend on the programme-participation rate (such as patient identification and recruitment), so that studies which did either not consider these cost and/or assumed a 100.0% participation rate may, in this regard, underestimate programme cost of LDCT-screening. This will be further discussed in the context of cost-factors relevant for LDCT lung cancer screening in Section 4.3 (research question 2).

Patient*innen-identifikation & -rekrutierung, sowie Beteiligungsrate an LDCT-Screening wichtig zu berücksichtigen

The costing-level also differs between the studies with respect to **diagnostic procedures.** Diagnostic procedures in Kumar et al. (2018) included, amongst others, biopsy, radiography, cytology, magnetic resonance imaging (MRI), pulmonary function tests/spirometry, thoracotomy, bronchoscopy, radionuclide scan/fusion positron emission tomography (PET) CT, etc. [27]. Based on primary data analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, Criss et al. (2019) included cost for follow-up exams, bronchoscopy, mediastinoscopy, needle-biopsy or video-assisted thoracoscopy, etc. [22]. In Cressman et al. (2017), diagnostic procedures were divided into non-invasive investigations (other imaging exams, human health resources and cardio-pulmonary tests) and invasive investigations (in particular, bronchoscopy and needle-biopsy) [30]. Guo et al. (2014) also distinguished between invasive and non-invasive diagnostic procedures but added human resource cost for a pre-diagnostic GP-time and diagnostic specialist time [36].

Diagnosekosten, z. B. für Biopsie, MRI, PET-CT

Table 4-9: Basic cost-components included in economic evaluations of LDCT-screening for lung cancer

General cost components	Examples
Screening	■ E.g., patient recruitment; screening test consultation; communication of results ■ Cost are usually assessed on a per-procedure level and assigned to each person participating in LDCT-screening.
Diagnostic procedures	■ E.g., interpretation of LDCT-screen; diagnostic follow-up; staging investigations; other diagnostic procedures, often further subdivided in: ■ *invasive diagnostic procedures, such as bronchoscopy, needle-biopsy, etc.* ■ *non-invasive procedures, such as other imaging technologies, cardio-pulmonary tests, etc.* ■ Cost are usually assessed on a per-procedure level and assigned to each person participating in LDCT-screening.
Treatment cost	■ E.g., surgery, chemotherapy, or radiotherapy ■ Cost of surgery are usually assigned as a one-off estimate per patient undergoing surgery. ■ Some studies differentiate treatment cost by cancer stage of progression.
Supportive and continuing care	■ E.g., inpatient and outpatient care, ongoing medication, surveillance ■ Some studies differentiate between supportive care cost immediately after surgery and ongoing supportive care. ■ Other studies differentiate continuing care cost by cancer stage of progression.
End of life treatment/palliative care	■ Typically assessed as for the past three to six months of life.

Abbreviations: LDCT: low dose computed tomography

Kosten der Patient*innenbehandlung nach Krebsstadium erhoben

In the analysed studies, **treatment cost** for lung cancer included those for surgical and non-surgical procedures, such as chemotherapy, radiotherapy, or clinician consultations. As the cost-effectiveness of LDCT-screening for lung cancer rests on the assumption of a stage shift through earlier diagnosis, stratifying cancer treatment cost by cancer stage appears to be warranted. Several studies (e.g., [11, 22, 24]) followed this approach. Toumazis et al. (2019) distinguished between surgical and non-surgical treatment cost, as well as, between the initial and continuing phase of care [23].

weiterführende Behandlungen ebenso nach Krebsstadien klassifiziert

Like with treatment cost, the **cost for supportive and continuing care** may also be stratified by cancer stage. Four studies [11, 22, 24, 32] followed this approach. Veronesi et al. (2020) did not make a distinction between treatment and continuing care cost, but they also stratified cost by cancer stage of progression [21].

Kosten der letzten 1-3 Lebensmonate teilweise berücksichtigt

Finally, most studies also included the **cost of end-of-life treatment and/or palliative care.** This rests on the assumption that the cost of lung cancer patients increase during their last months of life. Accordingly, Guo et al. (2014) estimated cost separately for the last three, two and one months before death [36]. Snowsill et al. (2018) included estimates for end-of-life care cost during the last 180 days before death [11], and Hofer et al. (2018) included cost of palliative care for the last model cycle (3 months) before death [25]. Hinde et al. (2018) assessed cost of palliative care by disease stage of progression [24], and Tomonaga et al. (2018) included terminal care cost for the last six month of life, which included treatment for recurrent or metastatic disease [28]. Toumazis et al. (2019) distinguished end-of-life care cost for the last six months before death between lung cancer deaths and death from other causes [23], whilst Criss et al. (2019) stratified terminal care cost both by cancer stage and end-of-life care cost for patients dying from other causes [22].

Data sources

Daten zum Ressourcenverbrauch & Kosten von klinischen Studien, administrativen oder Krankenhaus-Datensätzen oder aus anderen publizierten Studien

With respect to data sources for the cost of lung cancer screening, diagnosis and treatment, the studies under review can be generally categorised in three groups: those who estimated cost from administrative reimbursement or hospital data; those who used data from pilot studies, clinical trials or observational studies; and those who applied estimates sourced from reviewing the available literature. However, there is also a general distinction between the costing of the screening (and diagnostic) component, and that of subsequent lung cancer care, so that studies often apply a mixture of methods to source relevant cost information.

Rückerstattungsdaten in 3/13 Studien

As for reimbursement data, Gou et al. (2014) sourced cost information from the Ontario Case Costing Initiative from the Provincial Ministries of Health and Canadian Institute for Health Information [36]. Yang et al. (2017) applied NLST data for estimating resource use of screening, but reimbursement data of the Taiwan National Health Insurance (NHI) to obtain spending details for all the lung cancer cases between 2002 and 2013 [32]. Resource information for CT screening, diagnostic follow-ups, and complications were weighted with 2013 unit cost, also sourced from the NHI [32]. Toumazis et al. (2019) estimated screening and diagnostic cost from Medicare reimbursement rates, and lung cancer phase-specific cost from the related literature [23].

Krankenhausdaten in 4/13 Studien

With respect to hospital data, Tomonaga et al. (2018) extracted information from the Cancer Centre of the University Hospital Zurich [28]. The available information referred to 1,112 patients who were diagnosed between 2011 and 2015, and cost information was available from the beginning of 2012 until December 2015 [28]. The cost of screening and diagnosis was estimated from the Swiss tariff list for outpatient physician services and Swiss diagnostic related groups (DRG). LDCT data was also used to include an estimate for a centralised invitation of the eligible patients [28]. Veronesi et al. (2020) also used hospital data both for estimating screening and treatment cost, based upon a sample of 142 patients and including reimbursement rates for hospitalisations, outpatient appointments, examinations, and medications by year of diagnosis and disease stage [21]. Hinde et al. (2018) observed their estimates of resource use and unit cost directly from the Manchester lung cancer screening pilot [24]. Unit cost estimates were provided by University Hospital South Manchester, and the authors note that these estimates differ from National NHS Reference Costs as they represent the local costs rather than national averages [24]. Wade et al. (2018) use data from an Australian study of new cases of lung cancer in two hospitals in New South Wales, conducted between December 2005 and December 2006 [29]. Cost for an LDCT screen was based on the existing price of the test as listed in the 2015 Medicare Benefits Schedule. The cost of diagnostic workup for false-positive LDCT screen results was taken from the literature [29].

Daten von bestehenden Trials in 2/13 Studien

The studies that base estimates of resource use and cost on existing trials, include, for instance, Cressman et al. (2017), who use resource utilisation data from the Pan-Canadian Early Detection of Lung Cancer Study (PanCan) [30]. As their evaluation includes a societal perspective, they also based information on patient cost on data collected in the PanCan study, were participants at one recruiting centre completed questionnaires about their out-of-pocket expenses to attend screening appointments. Societal costs for patients receiving lung cancer treatment were also obtained through a survey [30]. Kumar et al. (2018) obtained resource use estimates from the NLST, and they weigh resources with 2016 Medicare reimbursement values for International Classification of Diseases [27].

Daten aus bestehender Literatur in 4/13 Studien

The remaining studies sourced information on resource utilisation and cost from the existing literature. Snowsill et al. (2018) stated that in the absence of directly applicable individual patient data on resource use, they conducted a literature search in MEDLINE to identify resource use and/or cost studies that might inform input parameters for their model [11]. They identified different sources for screening programme cost, hospital cost and end of life care from the literature. Literature-based estimates were also used by three other studies [22, 25, 26].

4.3 Cost-factors of LDCT-screening programmes for lung cancer

Lungenkrebs-spezifische Faktoren folglich beschrieben

The previous chapter focused both on general methodological characteristics of and costing methods used in health economic evaluations of lung cancer screening with LDCT. This chapter elaborates on lung screening-specific factors that may also determine intervention cost and outcomes (research question 2).

Liste von Kostenfaktoren, die v. a. bei LDCT-Lungenkrebs-Screening bedeutsam sind (Tabelle 4-10)

In their HTA-report, Black et al. (2006) discussed issues related to the construction of a model for the cost-effectiveness assessment of LDCT lung cancer screening, which includes a tabulation of the health-related cost required for the evaluation of lung cancer screening [5]. Based on this report and other sources, the project team developed a list of cost-factors particularly relevant for the economic evaluation of LDCT lung cancer screening and reviewed includable studies as to whether any of the identified factors have been explicitly evaluated. Results are provided in Table 4-10.

Effekt von Screening-teilnahmerate auf Kosten-Effektivitätsergebnisse

Screening participation may inflate the cost associated with a screening programme, in particular those components that relate to patient identification and recruitment. Black et al. (2006) argued, however, that the effect of screening participation on cost-effectiveness should be low unless drop-out occurs in subsequent screening intervals within programmes that are designed for continuous surveillance [5]. Indeed, increasingly poor participation rates in subsequent years may dramatically reduce the number of cases detected, which consequently worsens the ratio between intervention cost and health benefits [5]. Of the 13 analysed studies three [22, 23, 28] assumed perfect screening adherence (100.0%), which may lead to the abovementioned bias in favour of the intervention, especially considered that all three studies apply a lifetime horizon for continuous LDCT-screening. Seven studies under review considered less than perfect screening participation. Three studies [29, 30, 36] assumed screening participation based on NLST data of 70%, whilst Veronesi et al. (2020) based screening participation on findings from the COSMOS study [21]. Snowsill et al. (2018) assumed a probability that someone responds to the initial invite and returns the questionnaire of 0.307 and the probability someone joins the screening programme given they are eligible of 0.465 [11]. Jaine et al. (2018) assumed an LDCT-screening uptake per screening round in New Zealand of 0.7 in the general population and a lower uptake for the Maori subgroup of 0.64 [26]. Hofer et al. (2018) assumed screening participation of 0.54 in Germany [25].

Screening-Teilnahme variiert erheblich zwischen eingeschlossenen Studien

Table 4-10: Cost-factors in economic evaluations of LDCT lung cancer screening

Citation	Screening participation*	False-positive results	False-negative results	Inconclusive/ indeterminant screening results	Adverse events of diagnostic procedures	Incidental findings	Over-diagnosis bias	Length-bias	Lead-time bias	Investment cost	Administration, recruitment and overhead cost	Unrelated future medical cost	Direct non-medical cost	Indirect non-medical cost
Guo et al.,2014 [36]	Yes	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No	No
Yang et al., 2017 [32]	Not clear	Yes	No	No	Yes	No	No	No	Yes	No	No	No	No	No
Cressman et al., 2017 [30]	Yes	No	No	No	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes
Wade et al., 2018 [29]	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No
Tomonaga et al., 2018 [28]	No	Yes	No	No	No	Not clear	Yes	No	No	No	Yes	No	No	No
Snowsill et al., 2018 [11]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	No
Kumar et al., 2018 [27]	Not clear	No	No	No	Yes	No	Yes	No	No	No	No	Not clear	No	No
Jaine et al., 2018 [26]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Hofer et al., 2018 [25]	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No
Hinde et al., 2018 [24]	Not clear	Yes	No	No	No	No	No	No	Yes	No	Yes	No	No	No
Toumazis et al., 2019 [23]	No	Yes	No	Yes	No	No	Yes	No	No	No	No	No	No	No
Criss et al., 2019 [22]	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No
Veronesi et al., 2020 [21]	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	No	No	No

*Notes: * 'No' implies full screening participation*

falsch-positive Untersuchungsergebnisse → negativer Effekt auf Lebensqualität & erhöhter Ressourcen-verbrauch

False-positive screening results may impact on the HrQoL of individuals through anxiety related to a (false) lung cancer diagnosis and affect both cost and health outcomes through unnecessary diagnostic procedures, which in itself bear the risk of adverse health events *False-negative screening results* do, in the short term, not increase screening programme cost as no further investigations happen until the next screening interval or unless cancer becomes symptomatic, but in the longer run, bear the risk of late diagnosis, which could lead to the necessity of more radical treatment options and a poor prognosis Further to that, Black et al. (2006) described the effect of negative screening results on patient adherence to the programme, as some may perceive a negative test result as '*reinforcing their belief that their lifestyle does not require modification and that this will lead to reduced participation in screening programmes in the future*' ([5], p. 37). Hence, false-negative screening tests may lead to later diagnosis with the associated decrement in patient survival.

Parameter für LDCT-Sensitivität & Spezifität wichtig für gesundheits-ökonomische Modelle

To consider the effect of false-positive and false-negative screening results, an economic model needs to incorporate parameters of LDCT-screening sensitivity and specificity, as well as the related cost and health outcomes of those individuals receiving a false-positive or false-negative screening test result. All but four studies [22, 25, 27, 30] incorporated the effects of false-positive screening results on the cost-effectiveness of LDCT-screening for lung cancer, whilst only four studies [11, 21, 26, 36] also considered the impact of false-negative screens on cost-effectiveness results.

weitere Studien bzgl. unklaren Screening-Ergebnissen notwendig, z. B. bzgl. weiteren diagnostischen Tests oder der Abschätzung ihrer Auswirkungen auf Kosten-Effektivität

Whilst false-negative and false-positive screening results are conclusive but wrong, *inconclusive or indeterminant screening results* also require further diagnostic tests and may therefore increase per-patient cost, as well as the risk of adverse events from such diagnostic procedures. Three studies [11, 21, 23] incorporated the effects of inconclusive screening results on the cost-effectiveness of LDCT lung cancer screening. Snowsill et al. (2018) treated false-positive results and indeterminate findings equivalently in their model but acknowledged that indeterminate findings may be followed up less intensively than false-positive results [11]. Their model assumed a weighted average of these results according to UKLS findings and incorporates a temporary disutility of 0.063. Toumazis et al. (2019) modelled the cost-effectiveness of LDCT-screening and explicitly accounted for indeterminant findings, which they defined as '*positive CT-findings of unknown significance*' [23]. Their results were particularly sensitive to the disutility associated with indeterminant findings, and they concluded that '*efforts to quantify and better understand the impact of indeterminate findings on the effectiveness and cost-effectiveness of lung cancer screening are warranted*.' Veronesi et al. (2020) assumed that indeterminant findings which require further diagnostic tests would cost 10.0% of baseline screening cost of the COSMOS population and 5.0% in subsequent years [21].

diagnostische Tests → Gesundheitsrisiko → Berücksichtigung in gesundheits-ökonomischen Studien wichtig

Adverse events of diagnostic procedures may lead to deteriorated health outcomes of those individuals affected and also induce further resource use. Four of the 13 included studies [26, 27, 30, 32] modelled the impact of adverse events of diagnostic procedures on the cost-effectiveness of LDCT-screening for lung cancer. Cressman et al. (2017) estimated cost of adverse events related to LDCT-screening [30], whilst Yang et al. (2017) incorporated the cost of major and intermediate complications, as well as, the additional cost of radiation-induced lung cancer to estimate the cost-effectiveness of LDCT-screening for lung cancer in Taiwan [32]. Kumar et al. (2018) included five complication codes based on NLST-data, which showed a minimally significant difference between the two NLST-treatment groups [27]. Complications in-

cluded acute respiratory failure, hospitalisation post-procedure, pneumothorax requiring tube placement, bronchial stump leak requiring tube thoracostomy or another drainage for more than four days, and injury to vital organ or vessel [27]. Jaine et al. (2018) incorporated disability weights and cost of LDCT-screening-related complications [26].

LDCT-Screening kann zur Diagnose anderer Krankheiten führen → zusätzlichen Kosten & Auswirkungen auf gesundheitsbezogene Lebensqualität

LDCT-screening may also lead to the diagnosis of other diseases than lung cancer, namely **incidental findings**, which may lead to a referral to other specialists and subsequent treatment. Black et al. (2006) state that '*the extra costs and (dis)benefits of treating these conditions should be included in an economic evaluation of lung cancer screening´* ([5], p.49) and that '*each significant comorbidity will require a separate economic sub-model to be developed, and assumptions must be made about the extent to which this healthcare is additional expenditure'* ([5], p. 52). Three of the included studies considered the effect of incidental findings on cost-effectiveness results of LDCT-screening for lung cancer. Cressman et al. (2017) estimated the cost of incidental findings based on data from the PanCan-study defined as the additional cost of treating actionable incidental findings in the intervention study arm [30]. Wade et al. (2018) based their assessment on NLST data and assumed an average of 0.19 incidental findings per screening-participant [29]. They further assumed that that 80.0% of incidental findings occurred at the baseline scan and the other 20.0% evenly distributed over the second and third screening appointment [29]. Jaine et al. (2018) estimated incidental findings with clinical implications at 6.9–7.5% and the cost of incidental findings were estimated as the cost of one further imaging test and a specialist outpatient consultation [26]. However, the authors did not include the benefits and harms of incidental findings in their base-case analysis as for a lack of clear evidence in this area and they stated that if there was evidence of clinical benefits from incidental findings, the ICER would further improve.

Überdiagnose: einige klein & langsam wachsende Lungenkrebs-Erkrankungen vielleicht niemals symptomatisch → Behandlungen wären nicht notwendig

Over-diagnosis bias refers to a situation when LDCT-screening may detect cases which are small and slow-growing and therefore unlikely to become symptomatic during the remaining lifetime of a patient [5]. Detecting these cases may lead to unnecessary treatment, thereby increasing treatment cost without notable health benefits. Seven included studies considered the effect of over-diagnosis on the cost-effectiveness of LDCT-screening for lung cancer. Cressman et al. (2017) [30] assessed the effect of over-diagnosis in univariate sensitivity analysis and Tomonaga et al. (2018) [28] estimated the number of cases of the disease that would never have been detected if screening had not occurred, whilst Snowsill et al. (2018) found that participants in lung cancer screening may have a reduction in lung cancer mortality, but they do also receive more lung cancer diagnoses than without screening so that lung cancer is over-diagnosed [11]. Kumar et al. (2018) developed a multistage model that allowed considering the effect of over-diagnosis as patients screened would be assumed to transition more rapidly to a lung cancer diagnosis but more slowly from diagnosis to lung cancer mortality [27]. Jaine et al. (2018) removed the effect of over-diagnosis when modelling the stage shift within a two-step stage shift process [26], and Toumazis et al. (2019) estimated that 3.0% of the true-positive findings were over-diagnosed cases [23]. Criss et al. (2019) found that over-diagnosis increased with the upper age band for screening eligibility, with an average of 6.0% when applying the NLST and CMS criteria for screening eligibility, and 7.0% for USPSTF-criteria [22].

Length-bias: Diagnose von Patient*innen in früheren Krankheitsstadien, ohne Verlängerung der Überlebenszeit

Similar to over-diagnosis, which may be considered as an extreme form of *length bias*, the latter means that LDCT-screening leads to a diagnosis of more patients at earlier and less aggressive cancer stages who also have longer expected survival [5]. Identifying more patients with less aggressive disease may therefore bias estimated survival [5]. Conversely, if some cancers are more aggressive than others, they may reach the clinical stage earlier and may therefore not be detected by screening [11]. Only one study [11] considered the effect of length-bias on cost-effectiveness results.

Lead-time bias: Verzerrung der Ergebnisse einer gesundheits-ökonomischen Evaluation möglich

Lead-time bias means that lung cancer patients may be diagnosed earlier through LDCT-screening but their death occurs at the same time as it would have without screening. An earlier diagnosis may therefore extend the time between diagnosis and death, but not actual patient survival [5]. Five studies considered the effect of lead-time bias on cost-effectiveness results. Yang et al. (2017) adjusted for lead-time bias by assessing the difference in the loss of quality-adjusted life expectancy between LDCT-screened cases and radiography-screened cases after correction of the difference in age and sex at diagnosis [32]. The model developed by Snowsill et al. (2018) was predicated on the assumptions that screening-detected lung cancer leads to extended survival if diagnosed in an earlier stage than it would have presented clinically, but if the stage of screening-detected cancer is the same as if presented clinically, then the time to lung cancer mortality is extended by lead-time [11]. Jaine et al. (2018) tested different scenarios including an adjustment for lead-time and found that a change in lead time (base case 0.5 years) to zero and one year, respectively, has a moderate effect on ICERS [26]. Hinde et al. (2018) incorporated an estimate of the stage-specific time between the identification at screening and symptomatic presentation to adjust for lead-time bias [24], and Veronesi et al. (2020) adjusted for lead-time bias by adding two years to the life years of usual care for lung cancer cases [21].

1/13 Studien inkludierte Investitionskosten in Screening-Programme zur Abschätzung der Kosten-Effektivität

z. B. Kosten der Administration und Teilnehmer*innen-Rekrutierung sollten jedoch ebenfalls in gesundheits-ökonomischen Studien berücksichtigt werden

With respect to the LDCT-screening cost, investment cost include all those cost that are related to developing, implementing and scaling-up the screening programme. Only one study [26] considered the cost of initiating the screening programme. On the other hand, *administration, recruitment and overhead cost* include, for instance, the staff and premises required to identify potential participants, invite them into the programme, manage their records and progress through the pathway, as well as reimbursement to any other professionals involved in patient identification and recruitment. Seven studies considered administration, recruitment and overhead cost of an LDCT-screening programme for lung cancer in their health economic evaluations. Guo et al. (2014) included cost for physician recruitment and the communication of screening results to patients [36]. Tomonaga et al. (2018) included overhead costs such as capital costs, real estate and associated costs (including electricity, facility management and depreciation, and amortisation of inventory) [28]. Snowsill et al. (2018) considered overhead costs for admitted patient care, outpatients and emergency care through the use of NHS reference costs [11]. They also included estimates for administration, including the postal invitation for self-assessment to all potentially high-risk candidates, the scoring of questionnaires and a follow-up letter of invitation or decline [11]. Jaine et al. (2018) included direct cost per person invited to account for patient identification and invitation cost [26]. Hofer et al. (2018) added a lump sum of € 30 per case to represent the additional costs typically incurred in structured screening programs [25], and Hinde et al. (2018) included cost per invitation letter sent to potential participants [24]. Veronesi et al. (2020) added a lump

sum of € 17 per participant to account for administration and operational cost of the screening programme, based on unpublished COSMOS data [21].

Unrelated future medical cost are the cost of future illnesses, which are not related to lung cancer but happen due to the prolonged life expectancy as a result of the intervention. Only one study estimated the impact of unrelated future medical cost on the cost-effectiveness of LDCT-screening for lung cancer. Kumar et al. (2018) used NLST utilisation data and applied linear regression methods to estimate lifetime medical cost of lung cancer survivors, but it is unclear whether this estimation also includes unrelated future medical cost [27]. Jaine et al. (2018) assigned average citizen health system cost for each year alive to both, people in the screening and usual-care arms [26]. Accordingly, increased life-expectancy through LDCT-screening for lung cancer would also increase future medical care cost [26].

1/13 Studien inkludierte die Kosten zukünftiger Behandlungen für Krankheiten, die nicht mit Lungenkrebs in Verbindung stehen

Direct non-medical cost include all cost directly related to the disease but not incurred for the consumption of medical care, such as patient travel-cost or the cost for home-care. ***Indirect non-medical cost*** include productivity losses due to the disease. As both cost-components refer to a societal perspective, the only study under review that considered both is that by Cressman et al. (2017) [30].

direkte und indirekte nicht-medizinische Kosten wurden in 1/13 Studien berücksichtigt (gesellschaftliche Perspektive)

4.4 Results of economic evaluations on LDCT-screening programmes for lung cancer

The previous chapters reviewed general methodological characteristics, costing methods and relevant cost-factors for LDCT lung cancer screening as considered in the studies included. This chapter is concerned with research question 3 and reports on base-case results of economic evaluations (Section 4.4.1), results from sensitivity analyses (Section 4.4.2) and budget impact results (Section 4.4.3) of LDCT-screening for lung cancer. Some cost-factors that were considered on a more conceptual level in Section 4.3 may therefore appear again in Section 4.4.1 and, in particular, in Section 4.4.2, but with an emphasis on cost-effectiveness results from base-case and sensitivity-analyses reported in included studies.

im folgenden Kapitel Kosten-Effektivitäts-ergebnisse berichtet

4.4.1 Base-case results

Base-case results of economic evaluations on LDCT-screening provide a mixed picture of the cost-effectiveness of the intervention (Table 4-11). Whilst six studies [21, 22, 24, 25, 28, 32] were in support and reported ICERs lower than the cost-effectiveness threshold applied, one of those studies [21] (which also yields by far the lowest ICER for LDCT-screening versus no screening) is characterised by methods that considerably depart from other studies. Two studies [29, 30] were not in support of the intervention, and another five studies [11, 23, 26, 27, 36] reported mixed results for LDCT lung cancer screening.

Kosten-Effektivitäts-ergebnisse der inkludierten Studien nicht eindeutig:

Studies in support of LDCT-screening for lung cancer

6/13 Studien positives Kosten-Effektivitätsergebnis:

Schweiz: kosteneffektiv im Vergleich zu Grenzwert von EUR 50.000/LYG

Tomonaga et al. (2018) concluded that, when compared to a hypothetical threshold of EUR 50,000 per life-year gained, the implementation of LDCT-screening for lung cancer may be cost-effective in Switzerland [28]. When testing different eligibility criteria for screening (i.e., those from NLST and NELSON), their results were comparable. Whilst annual screening showed the highest health benefits, it also came at greater cost, but they suggested that, from a public health perspective, reaching higher benefits at increased cost (i.e., moving further up on the efficiency frontier) may be worthwhile [28].

Deutschland: kosteneffektiv im Vergleich zur Standardversorgung

The analysis conducted by Hofer et al. (2018) concluded that LDCT-screening for lung cancer is cost-effective compared to standard care in Germany [25]. However, whilst LDCT-screening for lung cancer yielded higher benefits for high-risk individuals, this also came at higher cost. Greater cost in high-risk individuals may be due to screening and diagnosis, treatment, and aftercare. The authors also concluded that biennial screening may be less cost-effective than annual screening [25].

UK, Manchester: kosteneffektiv (ICER GBP 10.069/ QALY gained)

The analysis conducted by Hinde et al. (2018) suggested that LDCT-screening for lung cancer, as implemented in their community-based pilot study in Manchester, is highly cost-effective, with a base-case ICER of GBP 10,069 per QALY gained [24].

Risikoselektion hat möglicherweise keinen Einfluss auf Kosten-Effektivität

Cressman et al. (2017), who tested targeted risk selection for annual LDCT lung cancer screening in Canada, came to the same conclusion for high-risk individuals [30]. However, they found that risk selection did not improve the cost-effectiveness of the LDCT intervention, but that the cost-effectiveness of LDCT-screening for lung cancer would further improve with more precise screening selection, fewer false-positive screening results and more effective early-stage treatment [30].

NLST & CMS Zulassungskriterien niedrigere ICERs als USPSTF-Kriterien

Criss et al. (2019) compared eligibility criteria for LDCT lung cancer screening from the NLST, CMS and UPSTF, and found that all three strategies produce ICERS below USD 100,000 per QALY [22]. Amongst the different screening strategies and the different models used in the analysis, NLST and CMS criteria appeared to be most cost-effective. The authors also concluded that the upper age limit of 80, as applied within the UPSTF-guidelines, would incur additional cost without notable health benefits [22].

Italien: niedriger ICER eventuell auf andere Methodik in der Studie zurückzuführen

Finally, as compared to the other studies under review, LDCT-screening for lung cancer produced a surprisingly low ICER in the study by Veronesi et al. (2020) with EUR 2944 per life-years gained and EUR 3297 per QALY gained [21]. The authors, therefore, concluded that LDCT-screening for lung cancer would be highly cost-effective, though it needs to be mentioned that this study does not just produce a considerably lower ICER than all other studies under review, but that there are also some substantial differences in study methodology, as described in the chapters above.

Table 4-11: Cost-effectiveness results of economic evaluations on LDCT lung cancer screening

Authors, year, reference	Screening Strategy	Incremental cost (base case)	Incremental effects (base case)	ICER (base case)	CE-threshold applied
Guo et al., 2014 [36]	■ **Annual screening** (Age: 55-75; pack years: ≥30) ■ **Biennial screening** (Age: 55-75; pack years: ≥30)	■ CAD 422,347,222 (CAD 1457.71 per LC-case detected)* ■ CAD 241,539,760 (CAD 839.71 per LC-case detected)*	■ 4589 QALYs (0.016 per LC-case detected)* ■ 3584 QALYs (0.012 per LC-case detected)*	■ CAD 92,025/QALY gained ■ CAD 67,396/QALY gained	CE-thresholds not established for Canada/Alberta
Yang et al., 2017 [32]	■ **3 annual screens** (Age: 55-75; pack-years: ≥30)	■ USD 22,755	■ 1.16 QALYs	■ USD 19,683/QALY gained	WHO-CHOICE threshold: (1*GDP/capita) = USD 20,925/QALY gained
Cressman et al., 2017 [30]	■ **Annual screening** (high-risk individuals based on risk scoring tool)	■ CAD 668	■ 0.032 QALYs	■ CAD 20,724/QALY gained	CAD 100,000/ QALY gained
Wade et al., 2018 [29]	■ **3 annual screens** (Age: 55-74; pack-years: ≥30; years since quitting: ≤15)	■ AUD 1564	■ 0.0113 LYS or 0.0067 QALYs	■ AUD 138,000/LYG ■ AUD 233,000/QALY gained	AUD 30,000 – 50,000/ QALY gained
Tomonaga et al., 2018 [28]	■ **Different screening scenarios** (based on age: 55 and 85; pack-years: 10-40; and NELSON/NLST eligibility criteria)	■ Between EUR 25,195,674 (triennial, NLST) and EUR 188,515,091 (annual, NLST) per 100.000	■ Between 1.009 (triennial, NLST) and 3.897 LYG (annual, NLST) per 100,000	■ Between EUR 24,972 (triennial, NLST) and EUR 48,369/LYG (annual, NLST)	Authors apply a tentative threshold of EUR 50,000/LYG
Snowsill et al., 2018 [11]	■ **Single screen** (Age: 55-75; 3% risk) ■ **Single screen** (Age: 60-75; 3% risk) ■ **Annual screen** (Age: 55-75; 3% risk) ■ **Biennial screen** (Age: 55-75; 3% risk) ■ **Tripple screen** (Age: 55-75; 3%risk)	■ GBP 26 ■ GBP 23 ■ GBP 75 ■ GBP 52 ■ GBP 39	■ 0.00091 QALYs ■ 0.00082 QALYs ■ 0.00067 QALYs ■ 0.00083 QALYs ■ 0.00103 QALYs	■ GBP 28,784/QALY gained ■ GBP 28,169/QALY gained ■ GBP112,853/QALY gained ■ GBP 63,129/QALY gained ■ GBP 38,375/QALY gained	GBP 20.000 – 30.000/ QALY gained
Kumar et al., 2018 [27]	■ **3 annual screens** (Age: 55-74; pack-years: ≥30; years since quitting: ≤15)	■ USD 1089	■ Benefits increased across increasing risk deciles: 0.015 to 0.056 LYG and 0.011 to 0.028 QALYs	■ All NLST-patients: USD 37,000/LYG or USD 60,000/QALY gained ■ Lowest-risk decile: USD 75,000/QALY gained ■ Highest risk decile: USD 53,000/QALY gained	USD 50,000 to USD 100,000/ QALY gained
Jaine et al., 2018 [26]	■ **Biennial screening** (Age: 55-74; pack years: ≥30; years since quitting: ≤15)	■ USD 2843	■ 0.067 QALYs	■ USD 44,000/QALY gained	GDP per capita as threshold: NZ$ 45,000 or USD 30,000
Hofer et al., 2018 [25]	■ **Annual screening** (Age: 55-75; cigarettes a day: ≥20) ■ **Biennial screening** (Age: 55-75; cigarettes a day: ≥20)	■ EUR 1153 ■ unclear	■ 0.06 LYG or 0.04 QALYs ■ unclear	■ EUR 19,302/LYG or EUR 30,291/QALY gained ■ EUR 24,594/LYG or EUR 38,694/QALY gained	Hypothetical threshold of EUR 48,000/ QALY gained (WHO)

Authors, year, reference	Screening Strategy	Incremental cost (base case)	Incremental effects (base case)	ICER (base case)	CE-threshold applied
Hinde et al., 2018 [24]	■ **Double screen** (Age: 55-74; indivdual 6 year risk: ≥1.51%)	■ GBP 15,788 (= GBP 663,076 per patient)*	■ 88.2 LYG and 65,85 QALYs (2.10 LYG and 1.57 QALYS per patient)*	■ GBP 10,069/QALY gained	GBP 20,000 to 30,000/ QALY gained
Toumazis et al., 2019 [23]	■ **Annual screening** (Age: 50-80, years smoking: 20; years since quitting: 20): ■ **Biennial screening** (Age: 60-70; years smoking: 40; years since quitting: 10)	■ USD 2391 ■ USD 282	■ 0.0294 QALYs ■ 0.0065 QALYs	■ USD 81,387/QALY gained ■ USD 43,118/QALY gained	USD 50,000 to 100,000/ QALY gained
Criss et al., 2019 [22]	■ **Annual** (Age: 55-74; NLST) ■ **Annual** (Age: 55-77; CMS) ■ **Annual** (Age: 55-80; USPSTF)	■ USD 870 ■ USD 930 ■ USD 980	■ 0.0265 LYG and 0.0199 QALYs ■ 0.0181 LYG and 0.0209 QALYS ■ 0.029 LYG and 0.0214 QALYs	■ USD 36,400/LYG and 49,200/QALY gained ■ USD 42,600/LYG and 68,600/QALY gained ■ USD 51,900/LYG and 96,700/QALY gained	USD 100,000/ QALY gained
Veronesi et al., 2020 [21]	■ 5 **annual screens** (Age: 55-77; pack-years: ≥30; years since quitting: ≤15)	■ EUR 254.94	■ 0.09 LYG and 0.08 QALY gained	■ EUR 2944/LYG and 3297/QALY gained	EUR 25,000/ QALY gained

*Abbreviations: AUD: Australian Dollar; CAD: Canadian Dollar; CE: Cost-effective; CMS: Centers for Medicare & Medicaid Services; EUR: Euro; GDP: Gross domestic product; LYG: Life-years gained; NELSON: Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST: National Lung Screening Trial; QALY: Quality-adjusted life-year; USD: US-Dollar; USPSTF: U.S. Preventive Services Task Force; WHO: World Health Organisation; Note: * own calculation.*

Studies not in support of LDCT-screening for lung cancer

2/13 Studien (Australien, England): negatives Kosten-Effektivitätsergebnis

Wade et al. (2018), who tested LDCT lung screening selection and implementation criteria in Australia, concluded that three annual LDCT screens are unlikely to be cost-effective in Australia [29]. Even when they applied exceptionally low screening costs, lung screening would not be cost-effective under their base-case assumptions [29].

LDCT-screening "kein kosteneffektiver Einsatz begrenzter Ressourcen im Gesundheitssystem"

Snowsill et al. (2018) concluded that, in the base-case analysis, LDCT-screening for lung cancer would not be cost-effective under the use of limited NHS resources at a threshold of GBP 20,000 per QALY gained [11]. Only at the higher threshold of GPB 30,000 per QALY gained and compared to no screening, two strategies may be cost-effective: a single screen for adults aged 60 to 75 with at least 3.0% lung cancer risk (ICER: 28,169 per QALY gained) and a single screen for adults aged 55 to 75 also at a minimum lung cancer risk of 3.0% (ICER: 28,784 per QALY gained). However, in a fully incremental analysis, only the former strategy was cost-effective. Snowsill et al. (2018) also performed an optimisation analysis and found that LDCT-screening for lung cancer would be most cost-effective compared to no screening adults 65 to 66 years with a 3.0% risk of lung cancer being offered triple screen (ICER: GBP 10,303 per QALY gained) [11]. However, the authors stated that the results from the optimisation analysis should be treated with significant caution [11].

Studies with mixed results

5/13 Studien: heterogene Kosten-Effektivitätsergebnisse

Guo et al. (2014) found that biennial screening was more cost-effective than annual screening with ICERS of CAD 67,396 per QALY gained and CAD 92,025 per QALY gained, respectively [36]. They concluded that LDCT-screening for lung cancer is not '*directly cost-effective*' (i.e., producing health benefits at lower cost). However, the Alberta Lung Cancer Screening Group concluded that the ICERs were acceptable and lung cancer screening was cost-effective. Nevertheless, for introducing the service one would have to disinvest from other services and ICERs of CAD 92,025 per QALY gained were considered high [36].

Kosten-Effektivität abhängig z. B. von:

Disutility unklarer Screening-Ergebnisse

Toumazis et al. (2019) compared ICERS against a cost-effectiveness threshold of USD 100,000 per QALY gained and found that, when assuming a 4.0% disutility from indeterminant findings, only biennial strategies were cost-effective [23]. Biennial screening for smokers aged 50 to 70 years, with at least 40 pack-years and less than ten years since quitting and coupled with the RADS lung guidelines had the highest health benefits. They concluded that the disutility associated with indeterminate findings impacts the cost-effectiveness of lung cancer screening and that more research on this matter is warranted.

Alter und Risikofaktoren

Ethnizität (z. B. Māori Bevölkerung)

Jaine et al. (2018) also found that compared to a cost-effectiveness threshold of USD 30,000 per QALY gained, LDCT-screening for lung cancer is unlikely to be cost-effective in New Zealand [26]. However, it may be cost-effective for the Māori population, who show a disproportionally high burden of disease from lung cancer [26].

Schwellenwert

Kumar et al. (2018) also tested risk targeting for LDCT lung cancer screening and found that although this may improve efficiency in terms of early lung cancer mortality per person screened, this would only modestly impact on life-years gained, QALYs gained and cost-effectiveness [27]. As with Snowsill et al. (2018) [11], none of the strategies tested met the lower cost-effective-

ness threshold of USD 50,000 per QALY gained, though all of them were below the upper threshold of USD 100,000 per QALY gained. Because higher risk participants required more invasive testing after a positive screen, the cost-effectiveness of screening higher-risk individuals was comparable to that of lower-risk participants. Thus, individual risk targeting did not improve the cost-effectiveness of LDCT lung cancer screening. Finally, the authors also acknowledged that their choice of comparator (i.e. chest x-ray) may have biased ICERs in favour of the intervention (i.e., no mortality benefit, but higher costs for chest x-ray) [27].

Wahl der Vergleichsalternative verzerrt womöglich Ergebnisse zugunsten von LDCT

Yang et al. (2017) found three consecutive annual LDCT-screens for lung cancer among high-risk smokers in Taiwan to be cost-effective at a threshold of USD 20,925 per QALY gained in 2013, which was calculated following WHO-CHOICE criteria (i.e. 1*GDP per capita) [32]. However, their base-case ICER of USD 19,683/QALY gained was close to their threshold and particularly sensitive to the cost of CT and the number of diagnostic follow-ups, and the authors do also acknowledge that their model did not take into account cases of possible over-diagnosis [32].

4.4.2 Results of sensitivity and scenario analyses

Zusammenfassung durchgeführter Sensitivitätsanalysen im Appendix

Cost-factors considered on a conceptual level in Section 4.3 were also subject to sensitivity and scenario analyses in reported studies. Results of these analyses are summarized below, whilst Appendix 8.4 (see Table 8-4) lists the type of sensitivity analyses reported by included studies together with main parameters, assumptions and scenarios tested. Though it is not within the scope of this review to discuss all results in detail, we will briefly report on the main findings. For further details, we refer to the original articles included in this review.

7/13 Studien probabilistische Sensitivitätsanalysen

All studies performed and reported on at least some form of univariate deterministic sensitivity analysis, and seven studies [11, 21, 22, 25, 29, 30, 32] also reported on probabilistic sensitivity analysis.

Relevant results from sensitivity analyses across studies relate to the disutility associated with false-positive screening results and inconclusive findings, screening-intervals and eligibility criteria, LDCT sensitivity and specificity, as well as screening cost input parameters.

unterschiedliche Faktoren berücksichgit, z. B. Disutilities der gesundheitsbezogenen Lebensqualität durch falsch-positive Testergebnisse → negative Effekte auf Kosten-Effektivität

For instance, Wade et al. (2018) found that the disutility value assigned to false-positive screening results had the greatest impact on the ICER of LDCT-screening for lung cancer, increasing it to AUD 509,000 per QALY gained when assigning a disutility weight of 0.5 for two months after the false-positive screening result [29]. Likewise, Snowsill et al. (2018) found that the impact of false-positive screening results and inconclusive findings on health-related quality of life were important determinants of interventions' cost-effectiveness [11]. Toumazis et al. (2019) assessed the impact of false-positive screening results in relation to screening intervals. They found that a 20.0% increase in false-positives applied to biennial screening (which showed more favourable ICERs in the base-case) would make annual screening (for which the authors kept false-positive rates fixed) for smokers between 55 and 70 years of age with at least 40 pack-years and less than ten years since smoking cessation the most cost-effective screening strategy [23].

Anteil unklarer Testergebnisse → Effekte auf Kosten-Effektivität einer Screening-Strategie

With respect to indeterminant findings, Toumazis et al. (2019) also found that a disutility weight of 1.0% or below would make biennial screening the cost-effective strategy with the highest health-benefit below a threshold of USD 50,000 per QALY gained [23]. At a higher threshold of USD 100,000 per QALY gained, annual screening was the cost-effective strategy with the highest health-benefit, but increasing the disutility of indeterminant findings above 2.0% would make biennial screening the cost-effective strategy with the highest health-benefit under any of the two thresholds [23].

zudem Screening-Intervalle, Screening-Frequenz, sowie die Einschlusskriterien für Screening-Programme → Effekt auf Kosten-Effektivität

In terms of screening intervals, frequency and eligibility criteria, Tomonaga et al. (2018) found that LDCT-screening cost-effectiveness was highly sensitive to smoking eligibility criteria and screening intervals [28]. Intervention cost were generally lower when LDCT-screening was performed less frequently and restricted to individuals at higher lung cancer risk. Triennial screening strategies, however, showed both lower cost and lower health benefits, as opposed to a biennial or annual screening [28]. Screening starting age also had a considerable impact on intervention cost, and Tomonaga et al. (2018) identified a U-shaped relationship between starting-age and cost-effectiveness of LDCT-screening. This, as the authors explained, is because starting screening at younger age increases cost but provides fewer additional health benefits (as lung-cancer incidence increases with age), whilst increasing starting age decreases intervention cost (as fewer people get screened), but also potential health benefits. Hofer et al. (2018) also found that screening intervals were an important determinant of intervention's cost-effectiveness and that, in their analysis, annual screening was more cost-effective as opposed to biennial programme specifications [25]. However, four other studies under review came to different conclusions with respect to the appropriate screening interval, usually resulting in annual screening to be the less cost-effective option [11, 36] [23, 28].

insbesondere die LDCT-Spezifizität großen Effekt auf QALYs

With respect to LDCT-screening test sensitivity and specificity, Snowsill et al. (2018) found that specificity appears to be a more important factor for LDCT-screening cost-effectiveness than sensitivity, but that improving either parameter would also improve cost-effectiveness [11]. Jaine et al. (2018) even identified test specificity as the most important factor for QALYs gained in their model, and (like Snowsill et al., 2018 [11]) concluded that this factor is more influential than screening test sensitivity [26].

Screening-Kosten häufig größten Effekt auf Kosten-Effektivität von Screening-Programmen

Moving on to cost-parameters of the models under review, Snowsill et al. (2018) found that the cost of LDCT-screens constitutes an influential factor for intervention cost-effectiveness, with ICERS decreasing with lower screening cost [11]. Wade et al. (2018) [29] and Jaine et al. (2018) [26] even identified the cost of screening to be the greatest influencer on the ICER of LDCT-screening for lung cancer. Yang et al. (2017) doubled the cost of LDCT-screening and found that the ICER increased to USD 31,066 per QALY gained, which would, under their assumed threshold value of USD 20,925 per QALY gained, render the intervention as not cost-effective [32]. On the other hand, doubling surgery cost had a much smaller effect on the ICER, increasing it to US 22,717 per QALY gained [32]. Hofer et al. (2018), also found that the cost of screening had a relatively large impact on cost-effectiveness, especially in their cost-utility analysis [25].

heterogene Ergebnisse hinsichtlich Teilnehmer*innenrate

Some studies found the impact of participation rates on the cost-effectiveness of LDCT-screening for lung cancer to be low or moderate [26, 30, 36]. Other studies showed a higher impact of patient participation on cost-effectiveness results [25], whilst Snowsill et al (2018) showed that a change in participation

rates may even lead to a change in location of various screening-programme specifications on the cost-effectiveness frontier [11].

weitere Untersuchungen bzgl. Einfluss von systematischer Risikoselektion auf Kosten-Effektivität von Screening-Programmen notwendig

Finally, some studies assessed the impact of lung cancer risk prediction on LDCT-screening cost-effectiveness. Snowsill et al. (2018) found that the performance of their risk prediction tool would positively affect cost-effectiveness [11], whilst Kumar et al. (2018) found, however, that a risk-stratified approach would yield the same screening decisions so that there would be no improvement in cost-effectiveness as compared to the NLST-inclusion criteria [27]. Rather, risk- stratification would identify some lower-risk individuals, but the (modest) savings from avoiding LDCT-screening in these individuals would be offset by the respective loss in QALYs [27]. Therefore, further research regarding the effect of risk prediction of LDCT-screening cost-effectiveness is needed.

4.4.3 Results from budget impact analyses

3/13 Studien berichten auch Budget-Impact-Ergebnisse, jedoch nicht im Detail:

The three studies that provided estimates of budget impact have all been included in the review of cost-effectiveness results reported above, as their primary aim was not to assess budget impact of LDCT lung cancer screening but rather its cost-effectiveness [21, 25, 36]. Consequently, the authors did not go into much detail about BIAs performed in their respective papers, and only described results in brief.

Kanada: Budgetauswirkungen für jährliches Screening mit ca. CAD 30 Millionen für die Jahre nach 2016

Guo et al. (2014) found that the budget impact for annual screening in 2012 in Alberta would be CAD 11.56 million and that this estimate would increase to CAD 32.88 in 2016 [36]. After 2016, the budget impact would remain stable at about CAD 30 million a year. For biennial screening, the budget impact would also increase until 2015 and remain stable afterwards, but the overall budget impact would be lower (CAD 309 million versus CAD 542 million over 20 years) [36]. The assessment was conducted from the Alberta health system perspective and extrapolated programme cost from 2012 to 2024, assuming a participation rate of 70.0%, a phase-in period of five years and Ontario cost estimates adjusted by the Alberta consumer price index [36].

Deutschland: inkrementelle Budgetauswirkungen von EUR 1.84 Milliarden (15 Jahre)

Hofer et al. (2018) estimated an incremental budget impact for LDCT lung cancer screening compared to standard care of EUR 1.84 billion in Germany, which would yield an estimated 95,581 LYS or 60,906 QALYs [25]. The analysis assumed a 15-year time horizon and a screen-eligible population of 1,600,270 people [25].

Italien: Budgetauswirkungen für 5 Jahre ca. EUR 600 Millionen

Finally, Veronesi et al. (2020) roughly estimated the budget impact of an LDCT lung cancer screening programme in Italy to be around EUR 600 million [21]. The estimation was based on a five-year time horizon, the assumption of 17,757,165 being in the eligible age-cohort, and of that 2,166,374 high-risk individuals eligible for screening.

Ergebnisse der Budget-Impact-Analysen sind nicht auf Ö übertragbar

It needs to be stated, however, that these estimates are not transferrable to the Austrian context, and as they are only very briefly described in the studies under review, it is not possible to assess, in more depth, their underlying assumptions, data and models. More research for the Austrian setting is therefore warranted.

5 Discussion

systematischer Review zu Methoden & Ergebnissen gesundheits-ökonomischer Studien zu LDCT-Lungenkrebs-Screening

This systematic review aimed to provide an update of the evidence previously reviewed by others (in particular Snowsill et al., 2018 [11]) on the cost-effectiveness, cost-utility and budget impact of lung cancer screening using LDCT versus no screening or screening with other imaging technologies in adult persons without confirmed or suspected lung cancer but at elevated risk. The research questions related to the methods that have been used to estimate the cost of lung cancer screening; the relevant cost-factors of lung cancer screening; and the results of existing economic evaluations of lung cancer screening in terms of cost-effectiveness, cost-utility, and budget impact.

& methodische Hilfestellung für mögliche zukünftige gesundheits-ökonomische Evaluationen in Ö

Ultimately, the aim was to provide an overview of the relevant evidence as to whether lung cancer screening with LDCT may have, in principle, the potential to be cost-effective in the Austrian context. However, the project team did not assess the potential to adapt or transfer existing study results to Austria. The aim was also to help to determine whether a model to assess the cost-effectiveness and/or budget impact of lung cancer screening with LDCT for Austria may be warranted, and to provide methodological guidance for such an exercise with a focus on the methods for appropriate cost-assessment.

13/25 Studien in qualitative Analyse eingeschlossen

The review identified 25 includable publications of which twelve were previously systematically reviewed by other authors. This update, therefore, included 13 publications in the qualitative synthesis.

im Folgenden Diskussion der gesundheits-ökonomischen Ergebnisse mit Hinblick auf Notwendigkeit eines österreichischen Models

In this chapter, we discuss the findings from the review exercise and put them further in context with the abovementioned research questions. Section 5.1 provides a discussion of economic evaluation results before section 5.2 summarises and appraises study characteristics, methods and relevant cost-factors of economic evaluations on lung cancer screening with LDCT. Section 5.3 is concerned with the strengths and weaknesses of this systematic review, and Section 5.4 concludes the discussion with recommendations for further research.

5.1 Summary and discussion of health economic results

heterogene Evidenz hinsichtlich der Kosten-Effektivität von Lungenkrebs-Screening-Programmen

Base-case results of economic evaluations on LDCT-screening provide a mixed picture on the cost-effectiveness of the intervention. Whilst six studies were in support and reported ICERs lower than the cost-effectiveness threshold applied by their respective authors, one of those [21] (which also yields by far the lowest ICER for LDCT-screening versus no screening) is characterised by methods that considerably depart from other studies. Two studies were not in support of the intervention, and another five studies reported mixed results for LDCT lung cancer screening. This finding is also in accord with the review of earlier studies (excluded from the qualitative synthesis of this systematic review update) conducted by Snowsill et al. (2018), who found that, even though there are several relevant studies on the cost-effectiveness of LDCT-screening for lung cancer available, their results are inconsistent in terms of the cost-effectiveness of the intervention [11]. Snowsill et al (2018)

further stated that other systematic reviews in the field also reported significant heterogeneity in cost-effectiveness results across relevant studies, and that drawing conclusions about the intervention would therefore be difficult, particularly when considering individual settings. This conclusion is consistent with the findings of this review exercise, and of particular relevance for the question of whether to adapt or develop a model for the Austrian context.

Studienergebnisse sprechen mehrheitlich für ein zweijähriges Screening-Intervall, jedoch nicht eindeutig

in österreichischem Modell unterschiedliche Screening-Intervalle zu testen

Of the five studies that compared different screening scenarios with respect to screening intervals, only one [25] found annual screening to be more cost-effective than biennial screening. The other four studies [11, 23, 28, 36] regarded biennial or triennial screening to be more cost-effective. Indeed, Snowsill et al. (2018) [11] found that biennial screening was more cost-effective than annual screening, but that triple screening was dominant compared to annual or biennial screening in all populations tested. Further, triple screening also led to the highest QALY-gain in all tested populations [11]. Sensitivity analyses performed by the authors of studies under review also showed the importance of screening intervals that intervention cost increased with shorter intervals, but so did potential health benefits. As shorter intervals appeared to be more effective but also more costly, it is therefore important to identify the appropriate interval given a respective (societal) willingness to pay for the service within the Austrian context.

zudem unterschiedliche Einschlusskriterien bzgl. Alter und Risikofaktoren für ein mögliches Screening-Programm anzudenken

Age groups tested in economic evaluations typically range between 55 and 75 years, and expanding LDCT lung cancer screening to very old age groups may not be cost-effective as the additional health benefits are likely to be low and offset by considerable additional cost for screening, diagnostic testing and subsequent treatment. Screening starting age was also tested in sensitivity analyses and found to be an important determinant of intervention cost-effectiveness. Starting screening programmes either too early or too late in terms of eligible age-cohorts may worsen cost-effectiveness because of the relationship between lung cancer incidence and age. This should also be tested in an Austrian model. The systematic review conducted by Snowsill et al. (2018) also found that a number of studies considered age and smoking history and found these to be influential for estimating the cost-effectiveness of LDCT-screening for lung cancer [11].

Einfluss von Instrumenten zur Risikoselektion für LDCT-Screening unklar

The use of risk assessment tools has been tested in few studies under review, but there is no clear evidence of whether the use of risk stratification tools may further improve the cost-effectiveness of LDCT lung cancer screening programmes. Studies that assessed the impact of risk-stratification on the cost-effectiveness of LDCT-screening found in scenario or sensitivity analyses either a positive impact on cost-effectiveness [11] or no impact as the cost savings from avoiding screening in low-risk individuals would be offset by the respective loss in QALYs [27]. Hence, further research on this matter may be warranted.

LDCT-Spezifizität hat größten Einfluss auf QALY-Zuwachs in 1 Studie

LDCT-screening test specificity was a more important factor for the cost-effectiveness of LDCT-screening for lung cancer as compared to test sensitivity, and from the two studies that reported respective sensitivity analyses, one even found test specificity to be the most important determinant for QALYs gained in the analysis. Hence, both factors should be tested in an Austrian model. Other important study findings related to the disutility of false-positive screening results and indeterminant findings, which some studies found to be important contributors to intervention cost-effectiveness.

Screening-Kosten erheblicher Faktor für Kosten-Effektivität

There was also strong agreement between studies that LDCT-screening cost was a very influential cost-parameter for the cost-effectiveness of the intervention, typically more important than other cost components (such as treatment, aftercare or continuing care). Earlier studies reviewed by Snowsill et al (2018) provide a similar picture [11].

Frage, ob Studien, welche wichtige Kosten-Faktoren nicht berücksichtigt haben, grundsätzlich bessere Kosteneffektivitätswerte aufweisen, auf Grundlage dieses Reviews nicht beantwortbar

An important question, which relates to both the cost-factors relevant for lung cancer screening with LDCT (research question 2) and ICERs reported by included studies (research question 3) is whether explicit consideration of various cost-factors, perhaps indicating a more thorough approach towards cost-assessment of lung cancer screening, also lead to more conservative cost-effectiveness estimates. Besides underlying theories and assumptions that should be reflected in respective model specifications (as elaborated in previous chapters), it is, unfortunately, not possible to answer this question with any degree of confidence. Indeed, in a purely hypothetical scenario, where a "common base-case" existed across studies under review, the direction and magnitude of change in ICERs with respect to relevant cost-factors of LDCT-screening for lung cancer could be assessed across studies under ceteris-paribus conditions. Alternatively, though quantitative pooling of economic data is generally not recommended ([13], p.9), an approach that has been empirically tested before would involve a meta-regression across includable studies [14, 15]. This, however, would rest on the availability of a sufficient number of data-points to allow for the assumption of random parameters, which is required to implement models that appropriately reflect complex data-structures as they typically arise when synthesising data from various studies. Further, as Boehler (2013) and Boehler and Lord (2016) have shown, variability within and across studies is likely to be vast, and it is difficult to identify the "appropriate set of covariates" to explain part of within- and between-study variation as well as variation across geographic contexts reflected in the dataset [14, 15].

Studienergebnisse hängen nicht nur von der Berücksichtigung relevanter Kostenfaktoren, sondern auch von zugrundeliegenden Daten, strukturellen Annahmen und anderen Faktoren ab

On the other hand, contentions based on a qualitative review of the evidence would also fail to provide meaningful answers to this question as ICERs do not only depend on the consideration of cost-factors (or combinations thereof) in a respective model, but also on the data used to feed model parameters, structural assumptions and other model specifications that may influence evaluation results. Without being able to control for these factors (for instance within the abovementioned meta-regression-framework), an answer cannot be provided. Having said all of this, one study under review, however, certainly stood out by reporting extraordinarily favourable ICERs for lung cancer screening with LDCT, and this study also departed from others in terms of some methodological characteristics, such as a particularly short time-horizon (five years) and differential discounting for cost (3.0%) and health benefits (0.0%) [21].

Interpretation von Studienergebnissen erfordert Kosten-Effektivitäts-Schwellenwert → erhebliche Variationen zwischen eingeschlossenen Studien & bisher für Ö nicht definiert

Similar to the systematic review of economic evaluations conducted by Snowsill et al. (2018), this review also identified a common theme across economic evaluations in the sense that LDCT-screening for lung cancer is both more costly and more effective than no screening [11]. This gives rise to the importance of another source of variation identified across studies, namely variation in applicable cost-effectiveness thresholds. Indeed, the interpretation of cost-effectiveness results reported in included studies, in particular, if they fall into the north-east quadrant of the cost-effectiveness plane, requires comparison against an appropriate threshold value, typically denoting the (societal) willingness to pay for a unit of health gain in a certain geographic setting. Whether LDCT-screening for lung cancer may or may not be regarded

as cost-effective, does therefore not only depend on the ICER estimated, but also on the cost-effectiveness threshold against which it has been compared by study authors. This threshold depends on the geographic context to which the study applies, and its value varied considerably between studies included for qualitative review. This variation in applicable cost-effectiveness thresholds, which further limits the geographic transferability of study findings, paired with the absence of a respective threshold-value for the Austrian context, make any contentions about the potential cost-effectiveness of LDCT-screening for lung cancer in Austria particularly difficult based on the evidence under review.

heterogene Studienlage bestätigt Notwendigkeit einer ökonomischen Evaluation für Ö

To sum up, the mixed evidence on the cost-effectiveness of LDCT-screening for lung cancer gives rise to the conduct of an Austrian study, and this conclusion is also supported by systematic reviews of earlier studies in the field, which stated that "*significant uncertainty remains as to the cost-effectiveness of LDCT screening for lung cancer*", and that „*the wide range of results from existing studies makes it challenging to draw conclusions*" ([11], p. 73). Even though we did not explicitly account for the geographic transferability of studies included to the Austrian context, it would therefore – based on the available evidence – be difficult to obtain a clear answer of whether LDCT-screening for lung cancer would have the potential to be cost-effective within the Austrian setting. The authors, thus, conclude that an economic evaluation of LDCT-screening for lung cancer for the Austrian setting is warranted.

5.2 Appraisal of study characteristics, methods and cost factors for an Austrian model

Study aims and methods

Studienbasis ist geeignet, um die vorab definierten Forschungsfragen zu beantworten

As this exercise provides an update of existing reviews of economic evaluations on LDCT-screening for lung cancer, all but one study included for qualitative synthesis were published since 2017. Indeed, there was a surge in publications on the topic in recent years, with 12 of 25 studies that met the general inclusion criteria published in the past three years. This is probably due to the publication of findings from the NLST-trial, which showed mortality benefits of lung cancer screening with LDCT [3]. The project team believes that the evidence base reviewed provides a good overview of both economic evaluation results and the methods that were used to generate them.

5/13 Studien aus Europa

Übertragbarkeit der Studienergebnisse nicht Teil dieses Berichts

Geographic coverage of studies was also wide. Of the 13 studies included for qualitative synthesis, five studies were conducted in the USA or Canada, three in Asia and New Zealand, and another five studies in Europe. Though there is a general notion that studies conducted outside Europe may be less transferrable to European countries than those conducted elsewhere in Europe, this claim cannot be supported without critical appraisal of studies' geographic transferability. However, as this was explicitly not part of this systematic review, it is therefore not possible to make contentions about the applicability of study findings to the Austrian context.

Einschlusskriterien auf Grundlage des klinischen Reviews (Part I) & im Rahmen von Sensitivitätsanalysen für Ö zu testen

Studies also varied in terms of screening-eligible populations. Whilst most studies regarded patients between 55 and 75 years eligible, some studies tested different screening-protocols by altering the starting and stopping ages for screening. In terms of risk factors, screening-eligible patients were mostly defined as current or former smokers with at least 30 pack-years of smoking and/or a maximum of 15 years since quitting. Again, some studies tested and compared different eligibility criteria with respect to risk factors, and others tested the use of risk stratification tools such as the $PLCO_{m2009}$ or $PLCO_{m2012}$ to identify and enrol patients who meet a pre-specified minimum risk-threshold. The clinical review of effectiveness and safety evidence conducted as Part I of this project should help to determine appropriate eligibility criteria for the Austrian context. These criteria should be tested against alternative assumptions within sensitivity and scenario analyses when developing an Austrian model.

Teilnehmer*innenraten, Kosten der Administration & Teilnehmer*innen-rekrutierung in gesundheits-ökonomischer Evaluation für Ö zu berücksichtigen

Though an integral part of screening programmes, most studies did not define and assess means of patient identification and enrolment. As evidence shows, however, patient participation in screening programmes is typically below 100.0%, which increases the relevance of this cost-component as several individuals need to be contacted to successfully recruit an additional participant into the programme. Studies which did make the cost of patient identification and enrolment explicit, considered, for instance, physician recruitment [36], a centralised invitation of all eligible patients [28], the screening of primary care records and subsequent patient recruitment through invitations sent from primary care units [11], or identification of patients from GP practices and assessment of screening eligibility with the $PLCO_{M2012}$ instrument [24]. An economic evaluation of LDCD-screening for lung cancer in Austria should be based on a pre-defined pathway of patient identification and enrolment into screening, which considers experiences and evidence from existing screening programmes in Austria and this pathway should also be thoroughly embedded within existing structures of healthcare provision. An Austrian model should further make reasonable assumptions with respect to screening participation rates, explicitly assess the cost related to identifying and recruiting patients into screening and test the sensitivity of results with respect to relevant input parameters.

Definition angemessener Screening-Intervalle für österreichisches Programm & Testung im Rahmen einer ökonomischen Evaluation

Intervention protocols also vary considerably across studies in terms of screening intervals and frequency, which is likely to impact both on cost, health outcomes, and cost-effectiveness of lung cancer screening with LDCT. Screening intervals range between annual and triennial. Whilst some studies assessed the cost and health outcomes of a one-off screening, two, three or five annual screens, others tested and compared annual, biennial, or triennial repeated screening over the entire age range of eligible individuals. An Austrian screening protocol should build upon the best available clinical evidence (Part I of this project), but also consider the findings of this review in terms of screening intervals and frequencies that have more favourable cost-effectiveness estimates across published studies.

Komparator „kein Screening" für österreichische gesundheits-ökonomische Evaluation angemessen

Finally, all but one study compared LDCT-screening for lung cancer against a no-screening alternative. This is also the most sensible choice of a comparator for LDCT lung cancer screening in Austria as there is currently no screening programme for lung cancer in place. Therefore, comparing LDCT-screening with other screening technologies (such as chest-radiography [27]) would bear the risk to underestimate the incremental cost of the intervention (compared to a no screening alternative), which may ultimately lead to unrealistically favourable ICERs for LDCT-screening.

General methodological characteristics

Mehrheit der Studien Gesundheitssystem-Perspektive, lebenslanger Zeithorizont, etc.

To sum up and appraise findings for general methodological characteristics to inform a potential de novo modelling exercise for lung cancer screening with LDCT in Austria, a majority of studies applied a healthcare system perspective, a lifetime horizon to assess interventions' incremental cost and health benefits, and non-differential discount rates for both cost and health outcomes.

für österreichische Evaluation Gesundheitssystem-Perspektive angemessen

Only one study [30] compared a public payer and a societal perspective. Though a societal perspective may be justified to assess the societal value of LDCT-screening for lung cancer, the inclusion of nonmedical indirect cost (in particular productivity losses) may bias results against population subgroups who are no longer actively participating in the labour market. This is particularly the case for patients eligible for lung cancer screening (typically patient cohorts with a starting age of 55 years or older and a stopping age between 75 and 85) so that a healthcare system perspective appears to be more appropriate for an Austrian modelling exercise.

Kosten & Gesundheitseffekte im Rahmen einer österreichischen Evaluation über einen lebenslangen Zeithorizont zu modellieren

Given the potential long-term impact of lung cancer screening with LDCT in terms of both cost and health outcomes, a lifetime modelling horizon seems to be the appropriate choice. Otherwise, potential stage-shift through earlier diagnosis (resulting in health utility gains), potential mortality benefits (resulting in prolonged life expectancy), but also potential future cost for prolonged lung cancer and supportive care may be misrepresented. Certainly, in this context, the five-year time horizon chosen by one study [21] seems to be inappropriately short.

Diskontsätze gemäß geltender Guidelines für Ö auf 5.0 % zu setzen

In terms of discounting, a non-differential rate of 3.0% has been applied in most studies in the base-case, whilst existing guidelines for Austria recommend the use of a 5.0% discount rate for both cost and health benefits, but including sensitivity analyses in the range of 3.0% to 10.0% [59]. Differential discounting, as it seems to be the method of choice in one study [21], may favour ICERs for lung cancer screening when future cost are being discounted but health benefits are not.

Möglichkeit anzudenken, existierendes Modell auf österreichischen Kontext zu adaptieren

When it comes to modelling methods for economic evaluations of lung cancer screening, LDCT, MISCAN and CISNET have a long-standing history of modelling cancer outcomes in general and the cost and health effects of cancer screening programmes in particular, including lung cancer. Indeed, CISNET currently consists of six modelling groups worldwide to develop, test and apply models to assess the cost and effects of lung cancer screening and tobacco control. Such existing models could be considered for adaption to the Austrian context.

Gesundheitseffekte des LDCT-Screenings mittels QALYs & LYG zu erheben

The disutility associated with lung cancer, the potential (dis-)utility of lung cancer screening (e.g., related to false-positive screening results or the consequences of evaluating abnormal findings, such as biopsy and/or surgery; radiation exposure; over-diagnosis; or patient distress and short-term psychological discomfort), and the potential health gains from LDCT-screening with lung cancer, both in terms of morbidity and mortality, appears to justify the measurement of health outcomes in terms of QALYs. Nevertheless, an approach that considers both, the cost-effectiveness (LYG) and cost-utility (QALYs) of lung cancer screening may prove informative for decision-makers.

& Health-state utilities mittels des EuroQol-5D Instruments

For estimating health state utilities, the EQ-5D instrument was the most common method of choice in studies under review. The EQ-5D is a widely used and validated instrument for the valuation of health states, which is also available in German language. However, it should be noted that there are currently no value-sets available for the Austrian context, so that a future study to estimate Austrian utility weights may be warranted.

zusätzlich quantitative Synthesen verfügbarer Studien verwenden

Finally, estimates of clinical effects are mostly based on the NLST trial, which demonstrated a mortality benefit of lung cancer screening with LDCT. An Austrian model should not only focus on NLST-trial data, but be based on a quantitative synthesis of the best available evidence (Part I of this review), and assess both heterogeneity and uncertainty within appropriate ranges.

Costing methods

Kostendaten & Ressourcenverbrauch für österreichisches Modell, z. B. von administrativen Datensätzen & Kosten der Lungenkrebs-Behandlung, sowie relevanter Anschlussbehandlungen getrennt nach Krebsstadium zu erheben

Basic cost-components for economic evaluations of LDCT-screening for lung cancer include screening cost, cost of diagnosis, treatment cost (e.g., distinguished by surgical cost and non-invasive treatment cost, as well as, by cancer stage of progression), supportive and continuing care cost (e.g., stratified by cancer stage of progression and time after surgery) and palliative care cost. As the cost-effectiveness of LDCT-screening for lung cancer rests on the assumption of a stage shift through earlier diagnosis, stratifying cancer treatment, supportive and continuing care cost by cancer stage of progression appears to be warranted. Some studies also stratified end-of-life care by cancer stage, and some of them further distinguished between end-of-life care cost for lung cancer and that for other-cause mortality. An Austrian model should therefore also consider the cost for treatment, supportive and continuing care stratified by disease stage. With respect to end-of-life care, at least a distinction between cancer-specific end-of-life care cost and other cause mortality cost appears to be warranted.

Nachteile der unterschiedlichen Kostendaten, z. B. Krankenhausdaten nicht generalisierbar

As reimbursement data provides a realistic picture of resource use and cost for a specific jurisdiction, it also contains potential inefficiencies that arise from routine use as opposed to more rigid protocols followed in clinical trials. For this reason, however, clinical trials may also lack external validity, as it is unlikely that their protocols provide a realistic picture of routine care. Cost information sourced from single hospitals, on the other hand, may not be entirely generalisable to a country level, as care routines differ between providers and regions. Information sourced from the literature should also be assessed carefully with respect to both its internal and external validity and its transferability to the jurisdiction of interest.

As for an Austrian model, cost information could be sourced, for instance, from administrative databases containing comprehensive reimbursement data from lung cancer patients with respect to inpatient and outpatient care, drug consumption and supportive care. If hospital databases were used, special consideration should be given to issues of extrapolation to a wider geographic context, including a critical assessment of variation in care pathways between healthcare providers and regions. Estimates sourced from the literature, unless Austria specific, may not provide the best source for resource use and cost information.

Relevant cost-factors

Teilnahmer*innenrate an Screening-Programmen zu beachten

Screening test participation rates should be incorporated as a parameter in an Austrian economic model for LDCT lung cancer screening, in particular in the case of a continuous screening programme. Low screening participation progressively limits the ability of a screening programme to detect lung cancers, especially in subsequent screening rounds, with detrimental effects on the cost-effectiveness of the intervention. Whilst some studies estimated the impact of participation rates on the cost-effectiveness of LDCT-screening for lung cancer to be low or moderate [26, 30, 36], other studies showed a higher impact of patient participation on cost-effectiveness results [25] or that changing screening uptake may even alter the position of alternative screening programme specifications on the cost-effectiveness frontier [11].

zudem Effekte falsch-positiver, falsch-negativer & unklarer Testergebnisse, sowie Risiken diagnostischer Tests auf die Kosten-Effektivität von LDCT-Screening auch in österreichischem Modell zu berücksichtigen

LDCT-screening sensitivity and specificity should also be modelled as parameters in an Austrian evaluation as studies which assessed these factors in respective sensitivity analyses demonstrated their potential impact on cost-effectiveness results. False-positive cases lead to anxiety and unnecessary diagnostic procedures, which bear additional risks for patients and increase intervention cost, and false-negative screening results may delay diagnosis until cancer becomes symptomatic, which potentially leads to poor prognosis and more radical treatment.

Inconclusive or indeterminant findings are positive screening results of unknown significance, which require further investigation. Indeterminant findings may both temporarily lead to disutility and increase healthcare cost through additional diagnostic procedures. Three studies assessed the impact of indeterminant findings on the cost-effectiveness of LDCT-screening which may increase screening programme cost through additional testing and result in (temporary) disutility for affected screening participants, both affecting the ICER of LDCT-screening for lung cancer. However, further research on this matter may be warranted. An Austrian model should therefore consider the explicit assessment of indeterminant findings

Diagnostic procedures bear the risk of adverse events, and four studies under review incorporated the cost or both cost and disutility of various complications. Only one of these studies reports that the extent to which adverse events of diagnostic procedures may impact on the cost and health effects of LDCT-screening for lung cancer may be rather low, so that further research may be warranted. An Austrian model should consider the inclusion of cost and health outcomes for complications due to screening, diagnostic procedures and care and test parameters in sensitivity and scenario analysis as further research on this matter may be warranted.

ebenso Kosten bzw. positive & negative Effekte von zufälligen Ergebnisse

It is reported that incidental findings occur frequently during LDCT-exams for lung cancer. Whilst three studies incorporated the cost of incidental findings in their analyses, none of them considered potential harms and benefits. Jaine et al. (2018) stated that this area warrants further research and that the ICER of LDCT-screening for lung cancer could further improve if the potential benefits of incidental findings were considered [26].

Auswirkungen von Length-bias, Lead-time-bias und Überdiagnose auch im Rahmen eines österreichischen Modells zu testen

An Austrian model should also consider the effects of different assumptions about length-bias, lead time and over-diagnosis within appropriate sensitivity and scenario analyses.

It is possible that an LDCT-screening programme for lung cancer would build upon existing capacities within an Austrian context, so that it is debatable whether investment cost should be considered, and if so, to which extend.

However, there is a reason for the inclusion of administration, recruitment and overhead cost of an LDCT-screening programme for lung cancer. An Austrian model should consider these cost so to develop a realistic model of LDCT-screening for lung cancer in Austria.

If LDCT-screening for lung cancer increases life-expectancy, this may also lead to higher unrelated future medical cost. It is debatable, however, whether these costs should be considered in an Austrian model, or more generally in economic evaluations for that matter.

Based on the findings and recommendations discussed above, an Austrian model for assessing the cost and health outcomes of LDCT-screening for lung cancer should be characterised by the features summarised in Table 5-1.

zusammenfassende Empfehlungen für Ö in nachfolgender Tabelle

Table 5-1: Summary of recommendations for an Austrian health economic model of LDCT-screening for lung cancer

Study characteristic	Recommendation
Population	■ **Age:** Population ages in studies included typically range between 55 and 75 years, and economic evaluation for Austria should test and compare different starting/stopping ages for screening. Results suggest that, in very old populations, potential health gains are lower and may be offset by the additional cost of screening and diagnostic testing. ■ **Risk factors:** Risk factors in studies are largely confined to smoking history, and economic evaluation for Austria should consider an assessment of different eligibility criteria (e.g. pack-years, time since smoking cessation, occupational risks, etc.). ■ Validated lung cancer **risk assessment tools** may have the potential to further improve the cost-effectiveness of LDCT-screening, and this option should be considered at least as a scenario within an Austrian model. However, cost-effectiveness results on the use of risk-stratification tools are mixed, and some studies suggested that they do not further improve the cost-effectiveness of LDCT-screening for lung cancer.
Intervention	■ **Patient enrollment:** Patient identification and recruitment should be based on experiences from existing screening programmes in Austria, thoroughly embedded within existing structures of healthcare provision, and reasonable assumptions should be made with respect to screening participation rates and related cost. ■ **Screening intervals:** Screening intervals typically range between annual and triennial, and a de novo model for Austria should consider different screening programme specifications based on both clinical and economic evidence. Four of five studies that compared different screening intervals concluded that biennial screening is more cost-effective than annual screening. ■ **Screening frequency:** Economic evaluations under review assess one-off, double, triple or repeated annual, biennial or triennial screenings. The optimal screening frequency for Austria should be based on the clinical review (Part I of this review) and different scenarios should be tested based upon the findings of economic evaluations reviewed in this report. There is no clear picture regarding the optimal screening frequency for the cost-effectiveness of LDCT-screening for lung cancer from the studies included.
Comparator	■ In the absence of a screening programme for lung cancer, the suitable comparator should be **'no screening'**, i.e. current standard care in Austria.
Perspective	■ For the base-case, a **healthcare system** perspective should be adopted for an Austrian model. ■ Scenario analysis may consider a societal perspective, although the inclusion of indirect nonmedical cost (i.e. productivity losses, informal care) is debatable.
Time horizon	■ The potential long-term impact of LDCT-screening on future cost and health benefits warrants a **lifetime perspective** for an Austrian model. ■ Because of the typical age-range of screen-eligible populations, a time horizon of **at least 25 years** should be considered.
Discount rates for cost and effects	■ A discount rate of **5.0%** for both, cost and health benefits should be adopted for the base case in an Austrian model, in accord with Austrian guidance for health economic evaluation [59]. ■ However, for sensitivity analysis, a range of discount rates **between 3.0% and 10.0%** should be tested and reported, which would also allow comparing results with existing international studies, which largely agree on discount rates for cost and health benefits of 3.0%.
Modelling	■ Before conducting an economic evaluation of LDCT-screening for lung cancer in Austria, a decision should be made as to whether to **adapt an existing model, such as MISCAN/CISNET, or** to build a **de novo model** for the Austrian context. ■ MISCAN and CISNET have a long-standing history of modelling cancer screening programmes with respect to both their cost and outcomes, including lung cancer screening.
Health outcomes	■ Health outcomes should generally be assessed in terms of **QALYs**. ■ An Austrian model could, however, report unweighted (LYS) and weighted (QALYs) results for LDCT lung cancer screening.

Study characteristic	Recommendation
Health state utilities	■ Based on the international evidence, preferably, the **EQ-5D** instrument should be used. ■ In the absence of an Austrian value-set, estimates from another jurisdiction would have to be adopted (such as those available for Germany). ■ A future study to estimate an Austrian value-set may be warranted.
Clinical effects	■ Estimates of clinical effectiveness should be based on a **quantitative synthesis of the best available evidence from RCTs** on lung cancer screening with LDCT as reviewed in Part I of this project. ■ Heterogeneity and uncertainty should be assessed through appropriate sensitivity analyses.
Methods of cost-assessment	■ **Resource use data:** Data for resource use should preferably be sourced from administrative databases which contain comprehensive information on inpatient and outpatient care for lung cancer treatment. ■ **Unit cost:** Should be based on Austrian tariffs. ■ **Basic cost-components** for economic evaluations of LDCT-screening for lung cancer include screening cost, cost of diagnosis, treatment cost, supportive and continuing care cost and palliative care cost. ■ Because of the anticipated **stage-shift** though LDCT-screening, the cost for treatment, supportive and continuing care should be stratified by cancer stage of progression (and perhaps also by time after surgery). End-of-life care may also be stratified by disease stage, at a minimum, however, these cost should be separately included for lung cancer deaths and deaths from other causes.
Relevant cost-factors	■ **Screening programme participation** is typically below 100.0% and may decrease further in subsequent screening intervals. Screening-programme participation should therefore be explicitly modelled, particularly in the case of continuous screening programmes, and parameters should be tested in a sensitivity analysis in an Austrian model. ■ Screening-test **sensitivity** and **specificity** should be incorporated in an Austrian model and parameters should be tested in sensitivity and scenario analysis. Otherwise, the cost and health effects associated with false-positive and false-negative test results may remain unclear. ■ The effect of inconclusive and **indeterminant findings** on both cost and health outcomes should be explicitly modelled in an Austrian model. ■ Screening, diagnostic and care-related **complications** should be assessed and their impact on cost-effectiveness results should be explored in sensitivity and scenario analyses. ■ The cost and potential health benefits of **incidental findings** should also be considered in an Austrian model of LDCT-screening for lung cancer. ■ An Austrian model should allow for the assessment of **length-bias** and **over-diagnosis** on the cost-effectiveness of LDCT-screening for lung cancer ■ An Austrian model should allow for the assessment of **lead-time bias** through appropriate sensitivity and scenario analyses. ■ **Patient recruitment, administration and overhead cost** should be considered.

Abbreviations: CISNET: Cancer Intervention and Surveillance Modelling Network; EQ-5D: EuroQol-5 Dimensions; LDCT: Low Dose Computed Tomography; LYS: Life Years Saved; MISCAN: MIcrosimulation SCreening Analysis; RCT: Randomised Controlled Trial; QALY: Quality Adjusted Life Year;

zusätzliche Budgetfolgenanalyse empfehlenswert

In addition to an economic evaluation, a budget impact analysis should also be considered for the Austrian context.

5.3 Strengths and Limitations

Stärken dieses Reviews:

stringente Definition und Anwendung von Methoden zur Literaturrecherche

Strengths of this systematic review update exercise on the economic evidence of LDCT-screening for lung cancer include the design and conduct of comprehensive database searchers for relevant publications performed by an experienced information scientist (TM) and supported through a thorough hand search of additional references performed by the lead-author (CB). Earlier systematic reviews did not identify any publications eligible for qualitative synthesis which were not also identified through the database searches performed (see Table 4-2). Indeed, of the twelve studies included in other systematic reviews, seven were excluded from review in this exercise as they were published before 2005, three studies were excluded because of their study design, one study as it focused on whole-body CT scan, and one citation was only available as a conference abstract.

Another strength of this exercise is that screening of titles and abstracts was performed independently by two experienced reviewers (CB and SW) and that agreement between both reviewers was generally high. Full-text review, data abstraction and narrative synthesis, on the other hand, was performed by one author (CB), but independently checked by the other author (SW) to minimise the risk of errors in study-selection, data extraction or qualitative synthesis of evidence. In addition to that, this report went through both an internal review by an independent AIHTA-researcher (IZK) and external review by an experienced health economist (AK), which may be regarded as another strength of this report.

systematisches Screening von Suchergebnissen durch zwei unabhängige Reviewer sowie interner und externer Review des Studienreports

On the other hand, this review only considered publications in English and German language, which may have resulted in missing relevant studies published in other languages, and there was no explicit quality assessment of studies included for qualitative synthesis. The latter point, however, was based on a deliberate decision by the project team as a major objective of this exercise was to learn about methods and cost-factors for the economic evaluation of lung cancer screening and this should include a critical discussion of the entire spectrum of economic evaluations and not just those considered of the highest quality. Nevertheless, the authors believe that inclusion and exclusion criteria specified in Table 3-1 ensured that at least some basic quality standards were met by studies includable for qualitative synthesis.

Schwächen dieses Reviews:

Beschränkung auf Literatur publiziert in deutscher oder englischer Sprache

Finally, it was not in the scope of this exercise to transfer or adapt published economic evaluation results to the Austrian context. Of the 13 studies included for qualitative synthesis, five studies were conducted in the USA or Canada, three in Asia and New Zealand, and another five studies in Europe. Though there is a general notion that studies conducted outside Europe may be less transferrable to European countries than those conducted elsewhere in Europe, this claim cannot be supported without critical appraisal of studies' geographic transferability. However, as this was explicitly not part of this systematic review, it is therefore not possible to make contentions about the applicability of study findings to the Austrian context. Results of published studies were rather reported in their original currencies and their original cost year. Currency conversion might have encouraged transferring cost-effectiveness results of LDCT screening to the Austrian context, which we believe would be highly speculative because of the various variability factors discussed throughout this report (e.g. considerable variation in methods across studies and contextual factors related to population, healthcare service provision and health system factors, amongst others) However, authors' conclusions based on comparison with locally applicable cost-effectiveness thresholds have been thoroughly discussed.

keine explizite Untersuchung der Übertragbarkeit von Studien auf Ö

5.4 Future research

With respect to further research, the first two questions to answer are whether to perform an economic evaluation for the Austrian context and if so, whether to adapt an existing model or to build a de novo model for Austria. In any case, an economic evaluation for Austria should consider both the cost-effectiveness/cost-utility of LDCT-screening for lung cancer, and its respective budget impact within an Austrian context.

bestehende & angepasste oder neue gesundheitsökonomische Evaluation für Ö?

ökonomische Evaluation von LDCT-Screening für Ö empfehlenswert

As for the first question, we believe that this review provided a clear indication in favour of conducting an economic evaluation for LDCT lung cancer screening in Austria as the evidence base is mixed and there is no clear indication as to whether the intervention or perhaps which specific programme specification would have the potential to be cost-effective in the Austrian setting. Without an Austrian model, contentions about the cost-effectiveness of LDCT-screening for lung cancer and the programme specification that is likely to yield the most favourable cost-effectiveness results would remain entirely speculative. In addition, there are numerous potential drivers of cost and health outcomes related to lung cancer screening with LDCT that may have been assessed in some studies, but never in combination so that a comprehensive assessment for the Austrian context is warranted.

MISCAN/CISNET potentielle Modell-kandidaten um auf Ö anzupassen

As for the second question, i.e. whether to adapt an existing model or to build a de novo model for Austria, this could be addressed in a pragmatic review of candidate models for adaptation, and whether the adaptation of an existing model would yield reasonably context-specific results at lower expected analytic resources. Certainly, the work in the context of MISCAN and CISNET is based upon a long-standing history of modelling cancer outcomes in general and the cost and health effects of cancer screening programmes in particular, including lung cancer. These models could therefore be assessed further as potential candidates for adaptation to the Austrian context.

weitere Forschung bzgl. Auswirkungen von Risikoselektions-instrumenten, zufälligen Befunden & einer Kombination aus Screening & Raucherentwöhnung nötig

Some questions related to the cost-effectiveness of LDCT-screening for lung cancer may also warrant further research when considering an economic evaluation for Austria. For instance, the use of risk assessment tools has been tested in few studies under review, but there is no clear evidence of whether the use of risk stratification tools may further improve the cost-effectiveness of LDCT lung cancer screening programmes. Likewise, the issue of incidental findings warrants further research before contentions regarding their impact on cost-effectiveness results can be made. Also, though not part of this review, further research could look into the combination of LDCT-screening for lung cancer with smoking cessation programmes. This may have the potential to further improve the cost-effectiveness of LDCT-screening for lung cancer and may therefore be assessed further.

verlässlicher Schwellenwert & EQ-5D Value-Sets für Ö erforderlich

In addition to the above, there are two more general issues related to economic evaluation in Austria that may warrant further research. First, the conduct of cost-utility analyses relies on the availability of validated value-sets for the target context. Currently, there are no EQ-5D value-sets available for Austria, and economic evaluations thus must rely on the transfer of value-sets from other countries. Hence, future research may consider the estimation of an Austrian value-set for the EQ-5D instrument. Finally, a threshold value against which results of an economic evaluation can be compared provides the decision rule upon which we can determine whether or not an intervention is cost-effective. In the absence of a threshold value for Austria, it is therefore difficult to make reliable decisions.

6 Conclusion

systematischer Review zu gesundheits-ökonomischen Analysen für LDCT-Lungenkrebs-Screening-Programme

This review aimed to provide an overview of both the methods used and the results reported by economic evaluations of LDCT-screening for lung cancer.

Lung cancer screening is a cost-intensive intervention, and introducing it on a population-level would depend on its likely budget impact and cost-effectiveness. A national rollout would require both sufficient willingness and ability to pay for the intervention, making lung cancer screening with LDCT generally more interesting in the context of higher performing and stronger funded healthcare systems.

Übertragbarkeit internationaler Ergebnisse auf Ö schwierig → gesundheits-ökonomische Analyse für Ö empfehlenswert

Given the considerable variation in both study methodology and results, however, it is currently not possible to make contentions about the potential cost-effectiveness of LDCT-screening for lung cancer. Studies are not just characterised by different assumptions about screening eligibility, screening intervals and frequency, but also by different data, models, costing methods, and consideration of screening-specific drivers of intervention cost and outcomes that would potentially affect the transferability of cost-effectiveness results of LDCT-screening to the Austrian context.

dafür notwendig: österreichische EQ-5D-Werte & Schwellenwert

An economic evaluation for the Austrian context is therefore warranted, together with the assessment of the potential budget impact of LDCT-screening. The methodological recommendations given in this report will hopefully guide researchers in the development of such a model, and ultimately help to establish whether LDCT-screening for lung cancer would be a good value for limited healthcare resources and affordable from a budget impact perspective in the Austrian context. Future research may also look into the development of an Austrian value set for the EQ-5D instrument, as well as the estimation of a threshold value to determine intervention cost-effectiveness in the Austrian context.

7 Literature

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8 Appendix

8.1 Inclusion criteria (PICO scheme)

Table 8-1: Inclusion criteria (PICO scheme)

Population	■ Adult persons (age 18 and older) without lung cancer (confirmed or suspected) at elevated risk of lung cancer ■ Risk factors: current or previous tobacco smoking, occupational toxins (e.g. radon, asbestos or fine particle exposure), COPD, lung fibrosis
Intervention	■ Various forms of lung cancer screening (such as organised/systematic screening, opportunistic screening, screening at various intervals) ▪ Low-dose chest computer tomography (LDCT) ▪ LDCT + biomarkers
Comparison	■ No screening ■ Screening for lung cancer using other imaging technologies, in particular, chest x-ray
Outcomes	■ Factors of direct and indirect cost of lung cancer screening, including treatment cost after a positive screening-test result as well as the cost of false-positive results ■ Methods of cost-estimation used in published studies ■ Cost-effectiveness estimates, such as incremental cost-effectiveness ratios (ICERs) and incremental net monetary benefits (INMBs) ■ Budget impact estimates
Study types	■ Health economic evaluations (CEA, CUA) ■ Budget impact analyses (BIA)
Publication period	■ From 2005 onwards
Language	■ German/English

Abbreviations: BIA: Budget impact analysis; COPD: chronic obstructive pulmonary disease; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; ICER: Incremental Cost-Effectiveness Ratio; INMB: Incremental Net Monetary Benefit; LDCT: Low Dose Computed Tomography

8.2 Items on data extraction form

Table 8-2: Items for data extraction

Item	Description	Data format
General study characteristics		
Main Author	Main author and publication year for identification	Short text
Year of publication	Publication year	Numerical
Research question	Brief summary of main research question addressed in the publication	Long text
CEA	Item to indicate whether CEA-results were reported (yes/no)	Binary, single selection permitted
CUA	Item to indicate whether CUA-results were reported (yes/no)	Binary, single selection permitted
BIA	Item to indicate whether BIA-results were reported (yes/no)	Binary, single selection permitted
Study country	Country to which study results apply	Short text
If applicable, region, province	If applicable, province or region to which study results apply	Short text
Currency	Currency in which cost and ICERs are reported	Short text
Timing of evaluation (price-year)	Price or cost year of study	Numerical
Funding	If reported, funding source(s) of the study	Short text
Funding, category	Categorisation of funding sources (public/private,industr/NGO, other)	Categorical, multiple selection permitted
Author affiliation/conflict of interest	If reported, statement of author affiliation and/or conflict of interest	Long text
Population characteristics and risk factors		
Age group	Lower and upper bound(s) of age cohort(s) subject to screening	Short text
Population risk factors	Risk factors of study population, in particular, smoking history (pack-years) and occupational risk factors	Short text
Intervention (screening) characteristics		
Patient identification and enrollment	How were eligible patients identified (e.g. use of risk stratification methods), including patient identification methods (e.g. opportunistic/disease registers etc.) and means of invitation/contacting patients?	Long text
LDCT-screening interval	Screening interval(s) (e.g. annual/biennial) and duration(s) of screening programme (e.g. one-off/three years/five years)	Short text
LDCT sensitivity & source (base case)	Estimated sensitivity of LDCT for lung cancer screening	Numerical (percentage)
LDCT Specificity (base case)	Estimated specificity of LDCT for lung cancer screening	Numerical (percentage)
Biomarker in addition to LDCT?	Were biomarkers used in addition to LDCT? (yes/no)	Binary, single entry permitted
Smoking cessation next to LDCT-screening?	Was smoking cessation part of the screening programme under assessment? (yes/no)	Binary, single entry permitted
Comparator characteristics		
Type of comparator(s)	Category of comparator (no screening/other screening technology/other screening programme specification(s))	Categorical, single selection permitted
Comparator description	Brief description of comparator	Long text

Item	Description	Data format
Outcome measurement		
Measurement of health outcomes	Category of health outcome measure(s) (life-years saved/QALYs/other)	Categorical, multiple selection permitted
If applicable: HrQOL instrument	If applicable, which HrQoL-instrument was used to value health outcomes	Short text
If applicable, source of health state utilities	If applicable, source of health state utilities (reference)	Short text
General methodological characteristics		
Perspective reported	What is the study perspective, as reported (Healthcare system/public payer/societal)	Categorical, multiple selections permitted
time horizon	What is the study/model time horizon	Short text
Discount rate benefits (base case)	Which discount rate was applied to benefits in the base case?	Numerical, percentage
Discount rate cost (base case)	Which discount rate was applied to cost in the base case?	Numerical, percentage
Analytic approach	What was the analytic approach of the study (i.e. model, individual patient data analysis from RCT/observational study)?	Short text
If applicable, type of model	Short description of the model, if applicable	Short text
If applicable, name/acronym of model	If a previously validated model was used, state name (and acronym) of the model	Short text
Source of clinical/effectiveness data (study name/acronym)	Which study was used to estimate clinical effectiveness data?	Short text
Costing methods		
General costing methodology	Brief summary of costing methods applied in the study	Long text
Resource data sources	Source(s) of resource use estimates for screening, diagnosis, treatment and (supportive) care	Long text
Unit cost data sources	Sources of unit cost estimates to value resource consumption	Long text
Screening Participation rate (base case)	Estimate of participation rate in screening programme	Numerical, percentage
Screening admin, recruitment and overheads considered?	Item to indicate whether authors incorporated cost of screening administration, recruitment and overheads (yes/no/unclear)	Categorical, single selection permitted
LDCT exam cost considered?	Item to indicate whether authors incorporated cost of LDCT exam (yes/no/unclear)	Categorical, single selection permitted
confirmation & diagnosis cost considered?	Item to indicate whether authors incorporated cost of confirmation and diagnosis (yes/no/unclear)	Categorical, single selection permitted
adverse events of diagnostic procedures considered?	Item to indicate whether authors incorporated cost of adverse events of diagnostic procedures (yes/no/unclear)	Categorical, single selection permitted
Follow-up cost of inconclusive screening results considered?	Item to indicate whether authors incorporated follow-up cost of inconclusive screening results (yes/no/unclear)	Categorical, single selection permitted
Explicit account of cost of false-positive results?	Item to indicate whether authors incorporated cost of false-positive results (yes/no/unclear)	Categorical, single selection permitted
Explicit account of cost of false-negative results?	Item to indicate whether authors incorporated cost of false-negative results (yes/no/unclear)	Categorical, single selection permitted
Curative surgery cost considered?	Item to indicate whether authors incorporated cost of curative surgery (yes/no/unclear)	Categorical, single selection permitted
Follow-up cost from surgery considered?	Item to indicate whether authors incorporated follow-up cost from surgery (yes/no/unclear)	Categorical, single selection permitted
Supportive and continuing care cost considered?	Item to indicate whether authors incorporated cost of supportive and continuing care (yes/no/unclear)	Categorical, single selection permitted

Item	Description	Data format
Cost of incidental findings considered?	Item to indicate whether authors incorporated cost of incidental findings (yes/no/unclear)	Categorical, single selection permitted
Cost of unrelated future medical care considered	Item to indicate whether authors incorporated cost unrelated future medical care (yes/no/unclear)	Categorical, single selection permitted
Investment cost considered?	Item to indicate whether authors incorporated initial investment cost to set up the screening programme (yes/no/unclear)	Categorical, single selection permitted
Direct non-medical cost considered?	Item to indicate whether authors incorporated direct non-medical cost (yes/no/unclear)	Categorical, single selection permitted
Indirect non-medical cost considered?	Item to indicate whether authors incorporated indirect non-medical cost (yes/no/unclear)	Categorical, single selection permitted
Cost of over-diagnosis considered?	Item to indicate whether authors incorporated cost of over-diagnosis (yes/no/unclear)	Categorical, single selection permitted
Lead-time bias considered?	Item to indicate whether authors incorporated lead time bias (yes/no/unclear)	Categorical, single selection permitted
Length bias considered?	Item to indicate whether authors incorporated length bias (yes/no/unclear)	Categorical, single selection permitted
Specific cost items considered in analysis	Tabulation of cost-items considered in cost analysis	Short text, new row for each item
Category of cost items considered?	Category of cost into which cost-items considered in analysis fall into	Categorical, single selection possible
Cost item definition	Definition of cost item (estimation procedure of cost-item, costing unit, etc)	Short text
Results, conclusions and limitations		
Incremental cost (base case)	Estimate of incremental cost in base case	Numerical & short text
Incremental effects (base case	Estimate of incremental cost in base case	Numerical & short text
ICER/Base case	Estimate of incremental cost-effectiveness ratio (ICER)in base case	Numerical and short text
CE-threshold applied	Cost-effectiveness threshold applicable in study country or threshold applied by authors to interpret study results	Numerical and short text
If applicable: BIA main results	Estimate of budget impact, if applicable	Numerical and short text
Conclusions	Main conclusions drawn by authors	Long text
major limitations stated	Major study limitations stated by authors	Long text
Sensitivity and scenario analysis		
Sensitivity analysis reported?	Did the authors perform and report sensitivity analyses? (yes/no)	Binary, single selection permitted
Type of sensitivity analysis	Which type of sensitivity analysis was reported? (deterministic/probabilistic)	Binary, multiple selection permitted)
Parameters & assumptions considered for Sensitivity/scenario analysis	Which parameters were considered for sensitivity analysis?	Long text
Main findings	Summary of main findings from sensitivity/scenario analysis	Long text
Comments		
Comments	Any further comments related to the study	Long text

8.3 Excluded studies after full-text review, with reason for exclusion

Table 8-3: Reasons for excluding studies after full-text review

Citation	Reason for exclusion
Bethune R, Wu L, Goodridge D, Osgood N, Tian Y, Sherin T, et al. The cost-effectiveness of lung cancer screening in Saskatchewan. Canadian Journal of Respiratory Critical Care and Sleep Medicine. 2017;1(2):102.	publication type: conference abstract
Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, et al. The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews. Health Technology Assessment (Winchester, England). 2006;10(3):iii-iv, ix-x, 1-90.	study design: systematic review
Black WC. Computed tomography screening for lung cancer in the National Lung Screening Trial: a cost-effectiveness analysis. Journal of Thoracic Imaging. 2015;30(2):79-87.	Duplication
Chien CR, Chen TH. Cost-effectiveness analysis of lung cancer screening with computed tomography. Value in Health 2009;12:A43.	Publication type: conference abstract
Chouaid C, Vella-Boucaud J, Pairon JC, Duburcq A, Detournay B, Boyer L, et al. Lung cancer screening program is cost-effective in french setting: A model-based study. Journal of Thoracic Oncology. 2017;12(1): p 470-S1.	Publication type: conference abstract
Chung JM, Simmerman EL, Sadek RF, Wojtowicz S, Dillard TA, Albo D, et al. Financial Analysis of Free Lung Cancer Screening Program Shows Profitability Using Broader NCCN Guidelines. Annals of Thoracic Surgery. 2019;107(3):885-90.	Study design: financial ROI analysis
Cressman S, Lam S, Tammemagi MC, Evans WK, Leighl NB, Regier DA, et al. Resource utilization and costs during the initial years of lung cancer screening with computed tomography in Canada. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2014;9(10):1449-58.	study design: cost analysis
Cressman S, Peacock S, Tremblay A, Ho C, Tammemagi M, Lam S. Implementing Lung Cancer Screening in Canada: Evidence on Adherence and Budget Impact from the Pan-Canadian Early Detection Study. Journal of Thoracic Oncology. 2018;13(10): p 959-S60.	publication type: conference abstract
Das P, Ng AK, Earle CC, Mauch PM, Kuntz KM. Computed tomography screening for cancer in Hodgkin's lymphoma survivors: decision analysis and cost-effectiveness analysis. Annals of Oncology. 2006;17(5):785-93.	Population: patients with confirmed cancer diagnosis
Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE, et al. UK Lung Cancer RCT Pilot Screening Trial: Baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax. 2016(b);71(2):161-70.	Duplication
Flores JP, Moreno-Koehler A, Finkelman M, Caro J, Strauss G. Cost-effectiveness analysis of CT vs chest X-ray (CXR) vs no screening for lung cancer (LC) in the PLCO and NLST randomized population trials (RPTS). Journal of thoracic oncology. 2017;12(1): p 354-S5.	publication type: conference abstract
Griffin E, Hyde C, Long L, Varley-Campbell J, Coelho H, Robinson S, et al. PCN248 Lung cancer screening by low-dose computerised tomography: A cost-effectiveness analysis of alternative programmes in the United Kingdom using a newly developed natural history based economic model. Value in Health. 2020;23:S66.	Publication type: conference abstract
Herold CJ, McLoud TC. Lung cancer screening: 360-degree review. Cancer imaging Conference: 15th annual teaching course of the international cancer imaging society, ICIS 2015 United kingdom. 2015;15.	Publication type: conference abstract
Horgan D. The European commission recommendations on lung cancer screening. Journal of Thoracic Oncology. 2017;12(11): p 1742.	Publication type: conference abstract
Hsieh H. Economic evaluation of lung cancer screening with low-dose computerized tomography (LDCT) for smoking groups in Taiwan. Value in Health. 2017;20(5): p 257.	Publication type: conference abstract
Jahn B, Todorovic J, Bundo M, Sroczynski G, Conrads-Frank A, Rochau U. Budget Impact Analysis of Cancer Screening: A Methodological Review. Applied Health Economics and Health Policy. 2019;17(4):493-511	intervention: not lung cancer-specific
Kanarkiewicz M, Szczęsny TJ, Krysiński J, Buciński A, Kowalewski J, Pawłowicz Z. Cost -effectiveness analysis of lung cancer screening with low-dose computerised tomography of the chest in Poland. Wspolczesna Onkologia. 2015;19(6):480-6.	Population: patients with confirmed LC diagnosis
Kuhlmann A, Treskova M, Aumann I, Golpon H, Vogel-Claussen J, Welte T, et al. Benefits, harms, and economic efficiency of low-dose CT lung cancer screening strategies in a population-based setting. Journal of Thoracic Oncology. 2017;12(11): p 1785.	Publication type: conference abstract
Lanni TB, Jr., Stevens C, Farah M, Boyer A, Davis J, Welsh R, et al. Early Results From the Implementation of a Lung Cancer Screening Program: The Beaumont Health System Experience. American Journal of Clinical Oncology. 2018;41(3):218-22.	study design: no economic evaluation
Marshall HM, Finn N, Bowman RV, Passmore LH, McCaul EM, Yang IA, et al. Cost of screening for lung cancer in Australia. Internal Medicine Journal. 2019;49(11):1392-9.	Study design: cost-analysis
Mastrangelo G, Ballarin MN, Bellini E, Bizzotto R, Zannol F, Gioffre F, et al. Feasibility of a screening programme for lung cancer in former asbestos workers. Occupational Medicine (Oxford). 2008;58(3):175-80.	Study design: cost-analysis

Citation	Reason for exclusion
Pedersen JH, Sorensen JB, Saghir Z, Flotten O, Brustugun OT, Ashraf H, et al. Implementation of lung cancer CT screening in the Nordic countries. Acta Oncologica. 2017;56(10):1249-57.	Study design: no economic evaluation
Priola AM, Priola SM, Giaj-Levra M, Basso E, Veltri A, Fava C, et al. Clinical implications and added costs of incidental findings in an early detection study of lung cancer by using low-dose spiral computed tomography. Clinical Lung Cancer. 2013;14(2):139-48.	Study design: cost analysis
Puggina A, Broumas A, Ricciardi W, Boccia S. Cost-effectiveness of screening for lung cancer with low-dose computed tomography: a systematic literature review. Eur J Public Health 2016;26:168–75. https://doi.org/10.1093/eurpub/ckv158	Study design: systematic review
Pyenson BS, Sander MS, Jiang Y, Kahn H, Mulshine JL. An actuarial analysis shows that offering lung cancer screening as an insurance benefit would save lives at relatively low cost. Health Affairs. 2012;31(4):770-9.	study design: perspective (commercial payer)
Rasmussen JF, Siersma V, Pedersen JH, Heleno B, Saghir Z, Brodersen J. Healthcare costs in the Danish randomised controlled lung cancer CT screening trial: a registry study. Lung Cancer 2014; 83: 347-55.	Study design: cost-analysis
Rasmussen JF, Siersma V, Pedersen JH, Heleno B, Zaghir S, Brodersen J. Health care costs in the randomized controlled danish lung cancer CT screening trial. Journal of thoracic oncology. 2013;8:S687.	Publication type: conference abstract
Raymakers AJN, Mayo J, Lam S, FitzGerald JM, Whitehurst DGT, Lynd LD. Cost-Effectiveness Analyses of Lung Cancer Screening Strategies Using Low-Dose Computed Tomography: A Systematic Review. Applied Health Economics and Health Policy. 2016;14(4):409-18.	Study design: systematic review
Roth JA, Ramsey SD. Computed tomography screening for lung cancer: A high-value proposition? JAMA – Journal of the American Medical Association. 2016;315(1):77-8.	Publication type: commentary/opinion
Roth JA, Sullivan SD, Goulart BH, Ravelo A, Sanderson JC, Ramsey SD. Projected Clinical, Resource Use, and Fiscal Impacts of Implementing Low-Dose Computed Tomography Lung Cancer Screening in Medicare. Journal of oncology practise/American Society of Clinical Oncology. 2015;11(4):267-72.	Study design: cost analysis
Veronesi G, Ghislandi S, Vanni E, Dieci E, Toschi L, Velutti L, et al. Analysis Indicates Low Incremental Cost-Effectiveness Ratio for Implementation of Lung Cancer Screening in Italy. Journal of Thoracic Oncology. 2018;13(10): p 968.	Publication type: conference abstract
Villanti AC, Jiang Y, Abrams DB, Pyenson BS. A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. PLoS ONE [Electronic Resource]. 2013;8(8):e71379.	Study design: perspective (commercial payer)
Wattson DA, Hunink MG, DiPiro PJ, Das P, Hodgson DC, Mauch PM, et al. Low-dose chest computed tomography for lung cancer screening among Hodgkin lymphoma survivors: a cost-effectiveness analysis. International Journal of Radiation Oncology, Biology, Physics. 2014;90(2):344-53.	Population: patients with confirmed cancer diagnosis
Weycker D, Boyle P, Lopez A, Jett JR, Detterbeck F, Kennedy TC, et al. Cost-effectiveness of screening older adult smokers for lung cancer with an autoantibody test (AABT). American Journal of Respiratory and Critical Care Medicine. 2011;183(1).	Publication type: conference abstract

8.4 Sensitivity and scenario analyses reported

Table 8-4: Overview of reported sensitivity and scenario analyses

Authors, year, reference	Type of sensitivity analysis performed	Main parameters & assumptions tested
Guo et al., 2014 [36]	■ Deterministic	■ Screening participation rate ■ Phase-in period
Yang et al., 2017 [32]	■ Deterministic ■ Probabilistic	■ Number of diagnostic follow-ups ■ Cost of LDCT ■ Cost of surgery ■ Stage distribution for CT-screening (NELSON instead of NLST) ■ Stage distribution of CT-screening (UKLS instead of NLST)

Cressman et al., 2017 [30]	■ Deterministic
	■ Probabilistic
		■ Screening mortality
		■ Curative treatment mortality
		■ Non–lung cancer mortality
		■ Non–curative treatment mortality
		■ Quality of life for screening participants without lung cancer
		■ Quality of life after curative treatment
		■ Non–curative treatment utility
		■ Screening participation
		■ Relapse rates
		■ Relapse costs
		■ Annual screening costs
		■ Non–curative treatment costs
		■ Curative costs
		■ In addition, the following parameters/scenarios were tested:
		  ■ Future high cost of oncology drugs
		  ■ Societal perspective
		  ■ Incidental findings
		  ■ Discount rates
		  ■ Higher postscreening lung cancer rates
		  ■ PanCan stage shift
		  ■ Risk stratification is not used to select NLST participants

Wade et al., 2018 [29]	■ Deterministic ■ Probabilistic	■ Other-cause mortality ■ Benefit of LDCT-screening included ■ NLST trial population weighted by QLCSS population and with age 55–59 years excluded ■ Cost per LDCT screen ■ Cost of a false-positive follow-up result ■ Cost of lung cancer diagnosis/treatment ■ Cost of stage III/IV NSCLC diagnosis/treatment ■ Cost of incidental findings ■ Disutility for false-positive scans ■ Only participants included with 40-year pack history ■ Definition of positive nodules on incidence screens ■ Discount rate ■ Time horizon (lifetime)
Tomonaga et al., 2018 [28]	■ Deterministic	■ Costs ■ Attendance rate ■ Discount rates ■ Scenario: UPSTF input values (cost) as well as NELSON and NLST

Snowsill et al., 2018 [11]	■ Deterministic
	■ Probabilistic
		■ All model parameters were subject to univariate sensitivity analysis.
		■ In addition, the following parameters/scenarios were tested:
		  ■ Age distribution
		  ■ Risk prediction accuracy
		  ■ Programme uptake
		  ■ Heterogeneity in tumour progression
		  ■ Mortality impact
		  ■ Short-term impact on utility from lung cancer diagnosis
		  ■ Alternative (significantly higher) disutility for stage IV lung cancer
		  ■ No screening anxiety after first screen

Authors, year, reference	Type of sensitivity analysis performed	Main parameters & assumptions tested
Snowsill et al., 2018 [11] *(continuation)*		■ No change in HRQoL for false-positive results ■ Follow-up care for up to 5 years ■ PSS costs for end of life not included ■ End-of-life costs excluded ■ Unit cost of LDCT ■ 10-year time horizon ■ No discounting
Kumar et al., 2018 [27]	■ Deterministic	■ Scenario 1: LDCT provides continually accruing lung cancer mortality gains by extrapolating the reduced hazard of lung cancer mortality throughout the patient's lifetime ■ Scenario 2: Age-specific background medical costs are removed ■ Scenario 3: Utility weight of 0.57 or 1.0 is assigned after a lung cancer diagnosis (base case, 0.77)
Jaine et al., 2018 [26]	■ Deterministic	■ Incidence of lung cancer ■ Proportion of population screened ■ Discount rates ■ Māori with equal uptake ■ Lead time ■ Stage distribution equal NLST data ■ No incidental findings ■ Screening test cost halved ■ Diagnostic test cost halved ■ High sensitivity (98.0%) and specificity (95.0%)
Hofer et al., 2018 [25]	■ Deterministic ■ Probabilistic	■ Lung cancer incidence ■ Screening cost ■ Time horizon ■ Screening interval (biennial) ■ Adherence ■ Early recall rates ■ Discount rates
Hinde et al., 2018 [24]	■ Deterministic	■ Survival times ■ Lead times
Toumazis et al., 2019 [23]	■ Deterministic	■ All model parameters were subject to univariate sensitivity analysis ■ In addition, the following parameters/scenarios were tested: ■ Disutility of indeterminate findings ■ False-positive rate ■ Cost-effectiveness of biennial screening strategies varying their false-positive rate value while keeping the false-positive rate for annual strategies fixed.
Criss et al., 2019 [22]	■ Deterministic ■ Probabilistic	■ Cost for LDCT examinations ■ Cumulative costs in the continuation phase of lung cancer treatment. ■ Treatment costs for persons younger than 65 ■ Screening adherence
Veronesi et al., 2020 [21]	■ Deterministic ■ Probabilistic	■ Cancer frequency in high-risk population ■ LDCT-screening sensitivity ■ LDCT-screening specificity ■ LDCT-screening, unit cost ■ LC treatment cost stage IA ■ LC treatment cost stage IB ■ LC treatment cost stage II ■ LC treatment cost stage III ■ LC treatment cost stage IV ■ False-positive workup cost ■ Life expectancy, stage IA ■ Life expectancy, stage IB ■ Life expectancy, stage II ■ Life expectancy, stage III ■ Life expectancy, stage IV ■ Lead-time bias correction stages III and IV ■ Lead-time bias correction stages I and II

Abbreviations: LC: Lung cancer; LDCT: Low dose computer tomography; NLST: National Lung Screening Trial; NELSON: Dutch-Belgian Randomized Lung Cancer Screening Trial;

8.5 Database searches of economic evaluations on lung cancer screening with LDCT

Search strategy for Medline

Database: Medline
Timeframe: 01.01.2005 to June 22, 2020
Data searched: June 22, 2020
Information Scientist: TM
Search hits: 166

Query Nr.	Search query	Hits
1	exp *Lung Neoplasms/ec [Economics]	533
2	((lung* or pneumo* or pulmon*) adj3 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or sarcoma* or neoplasm* or malignan*)).mp	385,832
3	Economics.fs	480,423
4	2 and 3	2,979
5	1 or 4	2,981
6	screen*.mp.	1,083,948
7	(chest adj2 (tomograph* or CT*)).mp.	20,622
8	LDCT*.mp.	1,364
9	exp Biomarkers/	913,485
10	biomarker*.mp.	798,783
11	6 or 7 or 8 or 9 or 10	2,194,511
12	Economics.fs.	480,423
13	11 and 12	24,265
14	exp Mass Screening/ec [Economics]	7,937
15	exp Tomography, X-Ray Computed/ec [Economics]	2,397
16	13 or 14 or 15	26,196
17	5 and 16	733
18	limit 17 to "all adult (19 plus years)"	316
19	limit 18 to (english or german)	297
20	limit 19 to yr="2005 – 2020"	240
21	remove duplicates from 20	166

Search strategy for Embase

Database: Embase
Timeframe: 01.01.2005 to June 20, 2020
Data searched: June 24, 2020
Information Scientist: TM
Search hits: 216

Query Nr.	Search query	Hits
1	'lung cancer'/exp	376,906
2	((lung* OR pneumo* OR pulmon*) NEAR/1 (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR 'adeno c*' OR sarcoma* OR neoplasm* OR malignan*)):ti,ab,kw,de	428,993
3	#1 OR #2	471,844
4	'screening'/exp	692,310
5	screen*:ti,ab,kw,de	1,335,586
6	'computer assisted tomography'/exp	1,090,422
7	'thorax'/exp	162,772
8	#6 AND #7	35,707
9	(chest NEAR/2 (tomograph* OR ct*)):ti,ab,kw,de	30,294
10	ldct*:ti,ab,kw,de	1,599
11	'biological marker'/exp	303,762
12	biomarker*:ti,ab,kw,de	417,372
13	#4 OR #5 OR #8 OR #9 OR #10 OR #11 OR #12	1,864,350
14	#3 AND #13	64,465
15	'economic evaluation'/exp	304,216
16	#14 AND #15	1,363
17	#16 AND ([adult]/lim OR [middle aged]/lim OR[aged]/lim OR [very elderly]/lim)	256
18	#17 AND ([english]/lim OR [german]/lim)	251
19	#18 AND [2005-2020]/py	216

Search strategy for Cochrane

Database: Cochrane
Timeframe: 01.01.2005 to June 24, 2020
Data searched: June 24, 2020
Information Scientist: TM
Search hits: 119

Query Nr.	Search query
1	MeSH descriptor: [Lung Neoplasms] explode all trees and with qualifier(s): [economics – EC]
2	((lung* OR pneumo* OR pulmon*) NEAR (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR sarcoma* OR neoplasm* OR malignan*)):ti,ab,kw (Word variations have been searched)
3	MeSH descriptor: [Mass Screening] explode all trees and with qualifier(s): [economics – EC]
4	(screen*):ti,ab,kw (Word variations have been searched)
5	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees and with qualifier(s): [economics – EC]
6	(chest NEAR (tomograph* OR CT*)):ti,ab,kw (Word variations have been searched)
7	(LDCT*):ti,ab,kw (Word variations have been searched)
8	MeSH descriptor: [Biomarkers] explode all trees
9	(biomarker*):ti,ab,kw (Word variations have been searched)

10	#10 #4 OR #6 OR #7 OR #8 OR #9 (Word variations have been searched)
11	MeSH descriptor: [Cost-Benefit Analysis] explode all trees
12	(cost* NEXT (minimi* OR effectiv* OR utili* OR benefi*)):ti,ab,kw (Word variations have been searched)
13	("economic evaluation*"):ti,ab,kw (Word variations have been searched)
14	(budget* impact*):ti,ab,kw (Word variations have been searched)
15	#11 OR #12 OR #13 OR #14 (Word variations have been searched)
16	#2 AND #15 (Word variations have been searched)
17	#1 OR #16 (Word variations have been searched)
18	#10 AND #15 (Word variations have been searched)
19	#3 OR #5 OR #18 (Word variations have been searched)
20	#16 AND #19 with Cochrane Library publication date Between Jan 2005 and Jun 2020 (Word variations have been searched)

Search strategy for CRD

Database: CRD
Timeframe: 01.01.2005 to June 24, 2020
Data searched: June 24, 2020
Information Scientist: TM
Search hits: 51

Query Nr.	Search query
1	MeSH DESCRIPTOR Lung Neoplasms EXPLODE ALL TREES WITH QUALIFIER EC
2	((lung* OR pneumo* OR pulmon*) NEAR (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR sarcoma* OR neoplasm* OR malignan*))
3	MeSH DESCRIPTOR Mass Screening EXPLODE ALL TREES WITH QUALIFIER EC
4	(screen*)
5	MeSH DESCRIPTOR Tomography, X-Ray EXPLODE ALL TREES WITH QUALIFIER EC
6	(chest NEAR (tomograph* OR CT*))
7	(LDCT*)
8	MeSH DESCRIPTOR Biomarkers EXPLODE ALL TREES
9	(biomarker*)
10	#4 OR #6 OR #7 OR #8 OR #9
11	MeSH DESCRIPTOR Cost-Benefit Analysis EXPLODE ALL TREES
12	(cost* NEXT (minimi* OR effectiv* OR utili* OR benefi*))
13	(economic* evaluat*)
14	(budget* impact*)
15	#11 OR #12 OR #13 OR #14
16	#2 AND #15
17	#1 OR #16
18	#10 AND #15
19	#3 OR #5 OR #18
20	#16 AND #19
21	(#20) FROM 2005 TO 2020

Search strategy for InaHTA

Database: InaHTA
Timeframe: 01.01.2005 to June 25, 2020
Data searched: June 25, 2020
Information Scientist: TM
Search hits: 2

Query Nr.	Search query	Hits
1	Lung Neoplasms"[mhe]"	203
2	lung* cancer*" OR "lung* tumor*" OR "lung* tumour*" OR "lung* carcinom*" OR "lung* adenom*" OR "lung* adenoc*" OR "lung* adeno-c*" OR "lung* sarcoma*" OR "lung* neoplasm*" OR "lung* malignan*""	264
3	pneumo* cancer*" OR "pneumo* tumor*" OR "pneumo* tumour*" OR "pneumo* carcinom*" OR "pneumo* adenom*" OR "pneumo* adenoc*" OR "pneumo* adeno-c*" OR "pneumo* sarcoma*" OR "pneumo* neoplasm*" OR "pneumo* malignan*""	0
4	pulmon* cancer*" OR "pulmon* tumor*" OR "pulmon* tumour*" OR "pulmon* carcinom*" OR "pulmon* adenom*" OR "pulmon* adenoc*" OR "pulmon* adeno-c*" OR "pulmon* sarcoma*" OR "pulmon* neoplasm*" OR "pulmon* malignan*""	0
5	Mass Screening"[mhe]"	612
6	screen*	1,078
7	Tomography Scanners, X-Ray Computed"[mhe]"	7
8	low-dose chest tomograph*	4
9	low-dose chest CT*	0
10	LDCT*	4
11	Biomarkers"[mhe]"	169
12	biomarker*	71
13	(pulmon* cancer*" OR "pulmon* tumor*" OR "pulmon* tumour*" OR "pulmon* carcinom*" OR "pulmon* adenom*" OR "pulmon* adenoc*" OR "pulmon* adeno-c*" OR "pulmon* sarcoma*" OR "pulmon* neoplasm*" OR "pulmon* malignan*") OR ("pneumo* cancer*" OR "pneumo* tumor*" OR "pneumo* tumour*" OR "pneumo* carcinom*" OR "pneumo* adenom*" OR "pneumo* adenoc*" OR "pneumo* adeno-c*" OR "pneumo* sarcoma*" OR "pneumo* neoplasm*" OR "pneumo* malignan*") OR ("lung* cancer*" OR "lung* tumor*" OR "lung* tumour*" OR "lung* carcinom*" OR "lung* adenom*" OR "lung* adenoc*" OR "lung* adeno-c*" OR "lung* sarcoma*" OR "lung* neoplasm*" OR "lung* malignan*") OR ("Lung Neoplasms"[mhe])	301
14	(biomarker*) OR (Biomarkers"[mhe]) OR (LDCT*) OR (low-dose chest CT*) OR (low-dose chest tomograph*) OR ("Tomography Scanners, X-Ray Computed"[mhe]) OR (screen*) OR ("Mass Screening"[mhe])"	1,337
15	((biomarker*) OR (Biomarkers"[mhe]) OR (LDCT*) OR (low-dose chest CT*) OR (low-dose chest tomograph*) OR ("Tomography Scanners, X-Ray Computed"[mhe]) OR (screen*) OR ("Mass Screening"[mhe])) AND (("pulmon* cancer*" OR "pulmon* tumor*" OR "pulmon* tumour*" OR "pulmon* carcinom*" OR "pulmon* adenom*" OR "pulmon* adenoc*" OR "pulmon* adeno-c*" OR "pulmon* sarcoma*" OR "pulmon* neoplasm*" OR "pulmon* malignan*") OR ("pneumo* cancer*" OR "pneumo* tumor*" OR "pneumo* tumour*" OR "pneumo* carcinom*" OR "pneumo* adenom*" OR "pneumo* adenoc*" OR "pneumo* adeno-c*" OR "pneumo* sarcoma*" OR "pneumo* neoplasm*" OR "pneumo* malignan*") OR ("lung* cancer*" OR "lung* tumor*" OR "lung* tumour*" OR "lung* carcinom*" OR "lung* adenom*" OR "lung* adenoc*" OR "lung* adeno-c*" OR "lung* sarcoma*" OR "lung* neoplasm*" OR "lung* malignan*") OR ("Lung Neoplasms"[mhe]))"	42
16	Cost-Benefit Analysis"[mhe]"	418
17	cost* minimi*" OR "cost* effectiv*" OR "cost* utili*" OR "cost* benefi*""	0
18	economic* evaluation*""	513
19	budget* impact*""	86
20	(budget* impact*") OR ("economic* evaluation*") OR ("cost* minimi*" OR "cost* effectiv*" OR "cost* utili*" OR "cost* benefi*") OR ("Cost-Benefit Analysis"[mhe])"	875
21	((budget* impact*") OR ("economic* evaluation*") OR ("cost* minimi*" OR "cost* effectiv*" OR "cost* utili*" OR "cost* benefi*") OR ("Cost-Benefit Analysis"[mhe])) AND (((biomarker*) OR ("Biomarkers"[mhe]) OR (LDCT*) OR (low-dose chest CT*) OR (low-dose chest tomograph*) OR ("Tomography Scanners, X-Ray Computed"[mhe]) OR (screen*) OR ("Mass Screening"[mhe])) AND (("pulmon* cancer*" OR "pulmon* tumor*" OR "pulmon* tumour*" OR "pulmon* carcinom*" OR "pulmon* adenom*" OR "pulmon* adenoc*" OR "pulmon* adeno-c*" OR "pulmon* sarcoma*" OR "pulmon* neoplasm*" OR "pulmon* malignan*") OR ("pneumo* cancer*" OR "pneumo* tumor*" OR "pneumo* tumour*" OR "pneumo* carcinom*" OR "pneumo* adenom*" OR "pneumo* adenoc*" OR "pneumo* adeno-c*" OR "pneumo* sarcoma*" OR "pneumo* neoplasm*" OR "pneumo* malignan*") OR ("lung* cancer*" OR "lung* tumor*" OR "lung* tumour*" OR "lung* carcinom*" OR "lung* adenom*" OR "lung* adenoc*" OR "lung* adeno-c*" OR "lung* sarcoma*" OR "lung* neoplasm*" OR "lung* malignan*") OR ("Lung Neoplasms"[mhe])))	2

Search strategy for Econlit

Database:	Econlit
Timeframe:	01.01.2005 to June 25, 2020
Data searched:	June 25, 2020
Information Scientist:	TM
Search hits:	7

Search query
(lung* OR pneumo* OR pulmon* OR pleur*) N10 (screen* OR tomograph* OR LDCT* OR biomarker* OR low-dose*))
Limiters – Published Date: 20050101-20200631 Expanders – Apply related words; Apply equivalent subjects Search modes – Boolean/Phrase Interface – EBSCOhost Research Databases Search Screen – Advanced Search

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH