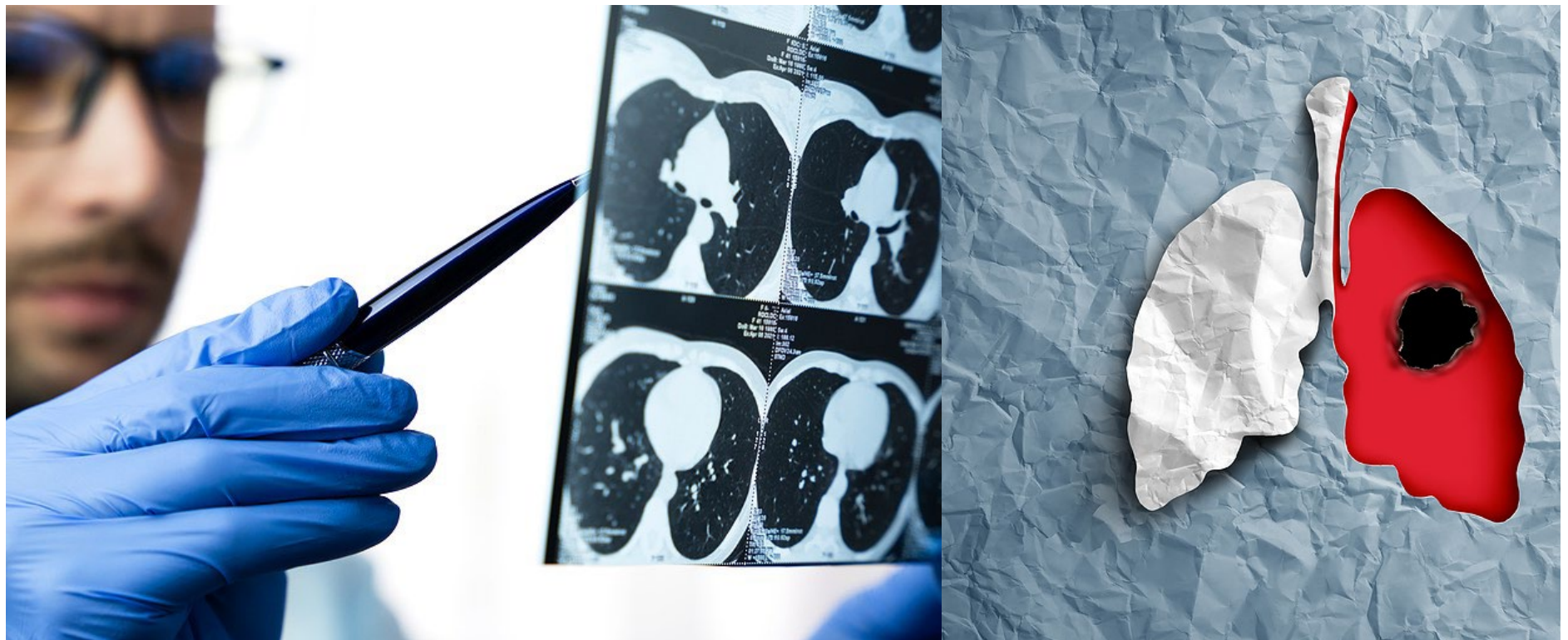


LUNG CANCER SCREENING IN A HIGH-RISK POPULATION



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AIHTA	Austrian Institute for Health Technology Assessment
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
ATC	Anatomical Therapeutic Chemical Classification
AU\$	Australian Dollar
BCR	Belgian Cancer Registry
BEIR	Biologic Effects of Ionizing Radiation
BMI	Body Mass Index
CAC	Coronary artery calcium
CADTH	Canadian Agency for Drugs & Technologies in Health
CanCORS	Cancer Core Outcomes Research and Surveillance Consortium
canSPUC	Cancer Screening Program in Urban China
CBA	Cost-benefit analysis
CCA	Cost-consequence analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CISNET	Cancer Intervention and Surveillance Modelling Network
CMA	Cost-minimisation analysis
CNY	Chinese yuan renminbi
COPD	Chronic Obstructive Pulmonary Disease
COS-LC	Consequences of Screening-Lung Cancer
COSMOS	Continuous Observation of Smoking Subjects
CRMM	Canadian Cancer Risk Management Model



CT	Computed Tomography
CTDIvol	Volume computed tomography dose index
CUA	Cost-utility analysis
CvKO	Centrum voor kankeropsporing
CXR	Chest x-ray
DANTE	Italian Detection And screening of early lung cancer by Novel imaging TEchnology trial
DDREF	Dose and dose-rate effectiveness factor
DEPISCAN	French randomized pilot trial of lung cancer screening
DEXA	Dual-energy x-ray absorptiometry
DLCST	Danish Lung Cancer Screening Trial
EAPC	Estimated annual percentage change
EBUS	Endobronchial ultrasound
EFOMP	European Federation of Organisations for Medical Physics
e.g.	Example given
ENaBL	Exeter natural history-based economic model of lung cancer screening
EQ-5D	European Quality of Life 5 Dimensions
ERS	European Respiratory Society
ESMO	European Society for Medical Oncology
ESR	European Respiratory Society
ESTI	European Society of Thoracic Imaging
ESTRO	European Society for Radiotherapy and Oncology
ESTS	European Society of Thoracic Surgeons
EUnetHTA	European network for Health Technology Assessment



EUS	Endoscopic ultrasound
FANC	Federal Agency for Nuclear Control
FARES	Fonds des Affections Respiratoires
FDG-PET	Fluorodeoxyglucose - Positron Emission Tomography
FP	False positive
GDP	Gross domestic product
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
HALYs	Health-adjusted life years
HANSE	Holistic implementation study Assessing a Northern German interdisciplinary lung cancer Screening Effort
HCP	Health care professional
HIS	Health Interview Survey
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HU	Hounsfield Unit
IAEA	International Atomic Energy Agency
IC	Incremental cost
ICD-O-3	International Classification of Diseases for Oncology, 3rd edition
ICER	Incremental Cost-Effectiveness Ratio
ICRP	International Commission on Radiological Protection
ICTRP	International Clinical Trials Registry Platform
IE	Incremental effects



IFs	Incidental findings
IHE	Institute of Health Economics
ILST	International Lung Screening Trial
IMA - AIM	Intermutualistic Agency
IN THE LUNG RUN	towards INdividually tailored INvitations, screening INtervals, and INtegrated co-morbidity reducing strategies in lung cancer screening
INAHTA	International Network of Agencies for Health Technology Assessment
INN - DCI	International nonproprietary name - Dénomination Commune Internationale
INSZ - NISS	Unique national security number
INWORKS	International Nuclear Workers Study
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRR	Incidence rate ratio
ISRCTN	International Standard Randomised Controlled Trial Number Registry
ITALUNG	Italian Lung Cancer Screening trial
IV	Intravenous
KCE	The Belgian Health Care Knowledge Centre
K-LUCAS	Korean Lung Cancer Screening project
KSZ-BCSS	Crossroad Bank for Social Security
LAR	Lifetime attributable risk
LC	Lung cancer
LCS	Lung Cancer Screening
LDCT	Low-dose computed tomography
LLPv2	Liverpool Lung Project lung cancer risk prediction model, version 2
LNT	Linear no-threshold



LSS	US Lung Screening Study
LUSI	German Lung Cancer Screening Intervention
LYG	Life-Year Gained
MAHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia
mGy	MilliGrays
MILD	Multicentric Italian Lung Detection trial
MRI	Magnetic Resonance Imaging
mSV	MilliSieverts
NA	Not available
NCCN	National Comprehensive Cancer Network
NELSON	Nederlands-Leuvens Longkanker Screenings Onderzoek
NHS	National Health Service
NIH	National Institutes of Health
NLM	National Library of Medicine
NLST	US National Lung Screening Trial
NRT	Nicotine replacement therapy
NS	Never smokers
NSCLC	Non-small cell lung cancer
NZ	New Zealand
NZ\$	New Zealand dollar
PanCan	Pan-Canadian Early Detection of Lung Cancer
PET	Positron Emission Tomography
PICO	Population, intervention, comparator, outcome
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial



PLCOM	Prostate Lung Cancer Colorectal and Ovarian Cancer Screening Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PY	Pack-years
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised controlled trial
RISP	The Italian Pulmonary Screening Network
RIZIV-INAMI	Rijksinstituut voor ziekte- en invaliditeitsverzekering – Institut National d'Assurance Maladie Invalidité
RR	Risk ratio
RT	Radiotherapy
RX	Radiography
SA	Sensitivity Analysis
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiation therapy
SBU	Swedish Council on Technology Assessment in Health Care
SC	Smoking Cessation
SCLC	Small cell lung cancer
SD	Standard deviation
SIMRISc	Simulation Model on Radiation Risk and breast cancer Screening
SMILE	Screening and Multiple Intervention on Lung Epidemics
SR	Systematic Review
STAI-6	State-Trait Anxiety Inventory
TBNA	Transbronchial needle aspiration



TKI	Tyrosine kinase inhibitors
TLCO	Transfer factor of the lungs for carbon monoxide
TNM	Tumour, Node, Metastasis
TP	True positive
UICC	Union Internationale Contre le Cancer
UK NSC	National Screening Committee of UK
UKLS	UK Lung Cancer Screening trial
US\$	American Dollar
US(A)	United States (of America)
USPSTF	US Preventive Services Task Force
VATS	Video-assisted thoracoscopy
VDT	Volume doubling time
VRGT	Vlaamse Vereniging voor Respiratoire Gezondheidszorg en Tuberculosebestrijding
WHO	World Health Organization
WSR	Age-standardised incidence rate using the World global standard population (expressed as the number of new cases per 100,000 person years)
WTP	Willingness-to-pay
y	years



■ SCIENTIFIC REPORT

1. INTRODUCTION

1.1. Lung cancer screening

Lung cancer is the second most frequently diagnosed cancer among both Belgian men (after prostate cancer) and women (after breast cancer), with a total of 9192 diagnoses in 2021.¹ It is the most common cause of cancer-related deaths and accounts for a major cause of disease and economic burden. According to the Belgian Cancer Registry (BCR), in 2021, about half of lung cancers in Belgium were diagnosed at stage IV, and more than 50% of all new lung cancer patients died within the first year after diagnosis.¹ Its management and prognosis largely depends on the stage at which it is treated, the 3-year relative survival rates for stage I and IV lung cancer were 80% and 13%, respectively, for diagnosis during 2017-2019.

There is a steep increase in drug expenditures for lung cancer since the start of reimbursement of immunotherapy in 2017. Whereas yearly total drug expenditures for non-small cell lung cancer (NSCLC, the most common type of lung cancer) were below €40 million before 2010, this amount more than tripled in 2017 to more than €120 million.² With high prevalence, poor prognosis and important healthcare expenditures, there remains a need for effective and cost-effective measures in order to reduce lung cancer burden.

A number of lung cancer risk factors have been identified, but tobacco smoking is the dominant cause of all major histological types of lung cancer and makes it a largely preventable disease.³ According to the last national Health Interview Survey (HIS) in 2018, about one in five (19.4%) Belgians aged 15 years and over smokes.⁴ As a consequence, control of tobacco use remains the most important and most cost-effective measure and holds the best prospect for reducing the burden of lung cancer. In Belgium, health promotion and disease prevention are under the responsibility of Federated entities,⁵ and behavioural smoking cessation support is partially reimbursed in the different regions and provided by certified tabacologists.⁶⁻⁸



In addition to smoking cessation interventions as a primary prevention strategy, screening with low-dose computed tomography (LDCT) scans has been suggested as an additional strategy aiming to detect lung cancer at an earlier stage and to reduce lung cancer mortality rates.⁹ The release of the results of the Dutch-Belgian Lung Cancer Screening trial (NELSON) in 2020 provided additional evidence that LDCT screening leads to a reduction of lung cancer mortality in high-risk individuals.¹⁰

As with all screening programs, not only benefits should be proven but the balancing of benefits, potential harms and cost-effectiveness considerations should be thoroughly assessed before starting implementation.⁹ As of December 9th, 2022, the European Council “invites member states to consider implementation of lung cancer screening, while assessing and taking decisions on the national or regional level depending on the disease burden and the healthcare resources available, the harm-benefit balance and cost-effectiveness of cancer screening, and experience from scientific trials and pilot projects.”¹¹

Currently there is no organised lung cancer screening program in Belgium, although initiatives have been taken in the Flemish region to progress towards its implementation. This report has been commissioned by a Flemish multidisciplinary working group of pneumologists, radiologists, thoracic surgeons, and radiotherapists (among others), and aims to provide on a national level the harm-benefit balance and cost-effectiveness of lung cancer screening.

1.2. Research questions

This KCE report aims to address the following research questions:

- What is the clinical effectiveness of lung cancer screening with low-dose CT in persons at high risk of lung cancer? Both the benefits (e.g., in terms of lung cancer-related and all-cause mortality, ...) and harms (e.g., overdiagnosis, false positives, radiation exposure, ...) are to be considered.
- What is the cost-effectiveness of a Belgian lung cancer screening programme with low-dose CT in persons at high risk of lung cancer?

- What ethical considerations should be addressed in lung cancer screening?

A budget impact analysis was part of the initial scope of this study, but ultimately could not be conducted within the available timeframe. It was decided to focus in this report on the safety/efficacy and cost-effectiveness of lung cancer screening. These elements determine whether it is useful from a clinical and efficiency point of view to support such a screening programme. If there is a willingness to introduce a lung cancer screening programme, then depending on the format of such a programme and supported by the info available in this report, a budget impact analysis can be further developed.

1.3. Target audience

This report is primarily intended for Belgian policymakers competent for public health and health care, both at the federal and regional level.

1.4. Methodology and structure of the report

To answer the aforementioned research questions, the following methods were used:

- A systematic review of the clinical effectiveness and safety of lung cancer screening using LDCT in persons at high risk of lung cancer (Chapter 3);
- A systematic review of the cost-effectiveness and cost-utility of lung cancer screening using LDCT in persons at high risk of lung cancer (Chapter 4);
- An analysis of Belgian lung cancer survival and costs data obtained via The Belgian Cancer Registry (BCR) and the Intermutualistic Agency (IMA-AIM) (Chapter 5), which serve as an input for the cost-effectiveness analysis;
- A Belgian cost-effectiveness and cost-utility analysis of lung cancer screening using LDCT compared to no screening (i.e., the current Belgian situation) (Chapter 6);



- A targeted literature review on ethical considerations of lung cancer screening (Chapter 7);
- Two face-to-face meetings (hereinafter called 'expert meetings') and where indicated email communication with medical professionals involved in lung cancer (e.g., pulmonologist, radiologist, radiotherapist, primary care physician), with experts involved in Belgian cancer screening programs and with patient representatives (see the colophon). During the expert meetings we presented preliminary results of the literature review on (cost-)effectiveness of lung cancer screening and presented the proposed methodology and inputs for the Belgian cost-effectiveness analysis.

This health technology assessment (HTA) is performed according to the procedures that are fully written out in KCE's Process Book.¹²

Prior to the aforementioned chapters, in Chapter 2, we provide the reader with some background information on lung cancer in Belgium and we present a concise overview of the general principles of cancer screening. In Chapter 8 we will provide an overall discussion of the most important findings, as well as a discussion of the strengths and limitations of the study.

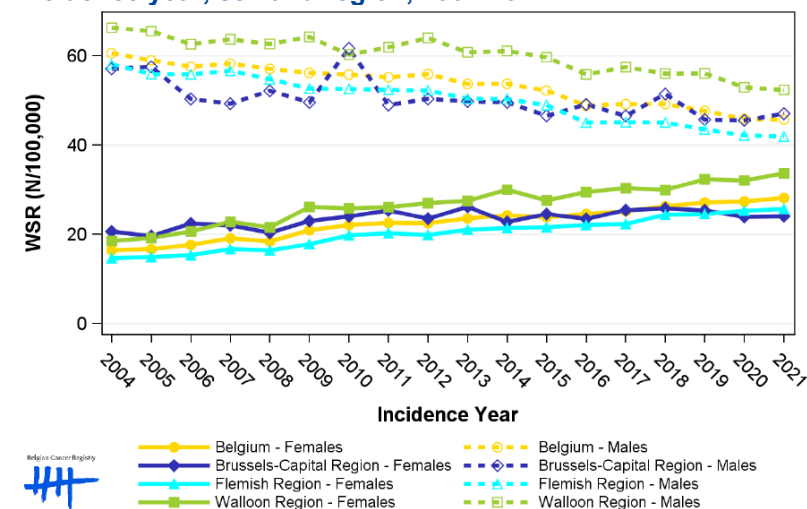
2. BACKGROUND

2.1. Lung cancer in Belgium

Incidence

Epidemiological data concerning lung cancer are provided by the Belgian Cancer Registry (BCR), a national and population-based cancer registry collecting data on a national level since the incidence year 2004. In Belgium, in 2021, a total of 9192 lung cancers were diagnosed: 5675 (62%) in men and 3517 (38%) in women.¹ Between 2007 and 2021, the age-standardised incidence of lung cancer among women increased by 47%, whereas it decreased by 22% among men. This results in converging lung cancer age-standardised incidence rates between sexes, as observed in Figure 1. Lung cancer incidence is strongly related to age, age-specific incidence rates rise from around age 45-49 years and drop in the oldest age groups (Figure 2).¹

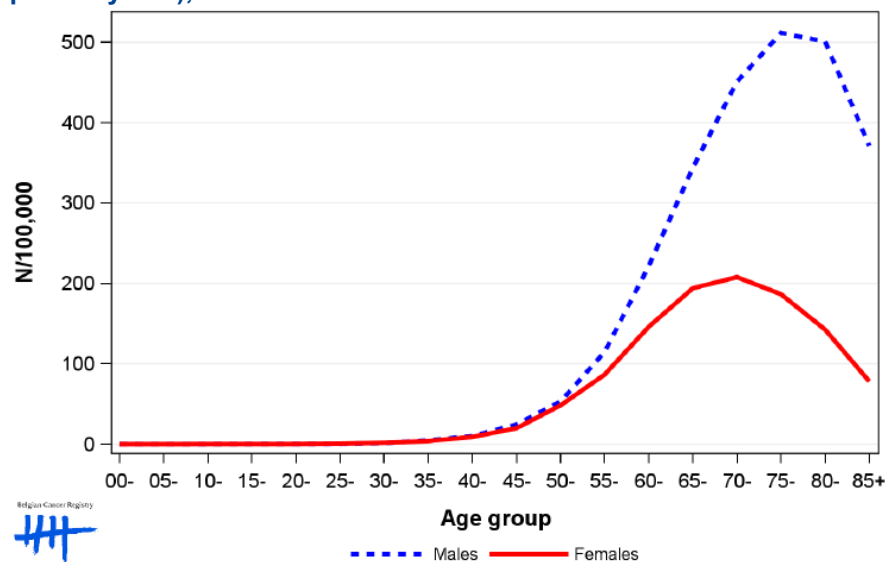
Figure 1 – Age-standardised lung cancer incidence rates (WSR) by incidence year, sex and region, 2004-2021



Source: Belgian Cancer Registry (BCR)¹



Figure 2 – Lung Cancer Age-specific incidence rates by sex (n/100 000 person-years), 2017-2021



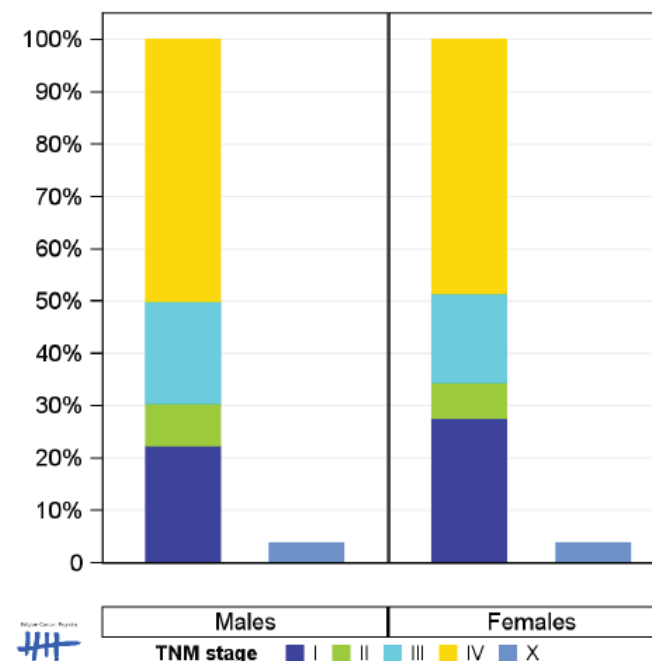
Source: Belgian Cancer Registry (BCR)¹

Histology and staging

Non-small cell lung cancer (NSCLC) is the most frequent histological type of lung cancer in Belgium, accounting for 3 out of 4 primary lung cancers, whereas small cell lung cancer (SCLC) accounts for about 15%.¹³ Lung adenocarcinoma is a type of NSCLC and is the most common lung cancer both in men and women, with a gradually increasing incidence in the latter.¹⁴ The TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (Union Internationale Contre le Cancer - UICC) is the established, uniform method of staging lung cancer. TNM systematically describes the extent of malignancies - primarily on their anatomy - and categorizes each malignancy by the features/extent of the primary tumour (T), regional lymph node(s) involvement (N), and distant metastases (M). The BCR database provides accurate data on lung

cancer stage distribution according to the TNM (Tumour, Node, Metastasis) 8th edition that was published in 2017.¹⁵ In 2020, 96% of newly diagnosed lung cancers were staged, which is of importance in the view of this study, as lung cancer screening aims to downstage -to detect lung cancers at an earlier stage- and accurate stage distribution data are needed in cost-effectiveness modelling. Figure 3 shows the distribution of lung cancer TNM stages in men and women in Belgium for 2020, with a comparable pattern between sexes.¹

Figure 3 – Bar chart of lung cancer combined stage by sex, Belgium 2021



Combined TNM stage : compilation of pathological (pTNM) and clinical (cTNM) stage. pTNM prevails over cTNM, except when cTNM stage is IV
Stage X: diagnoses with an unknown stage
Source: Belgian Cancer Registry (BCR)¹



Mortality and survival

A total of 5849 patients died of lung cancer in Belgium in 2019, making it the most important cause of cancer-related death in men and the second in women after breast cancer. In 2020, lung cancer was the third most important cause of premature death^a in men (after suicide and COVID-19) and the second cause of premature death in women (after breast cancer).¹⁶

The 5-year relative survival proportion for lung cancer between 2017 and 2021 is 23.6% in men versus 32.1% in women. Survival is inversely related to age in both sexes, with a 5-year relative survival of 21% and 28% of men and women aged 65 and more, respectively.¹ Stage at diagnosis (TNM staging) is a strong predictor of survival, as illustrated by showing the relative survival curves of patients with lung cancer by stage. For stage I NSCLC, the average 3-year survival probability was almost 80% in the incidence years 2014 to 2017; whereas for stage IV NSCLC this was only 15%.²

Risk factors for lung cancer

Both modifiable and non-modifiable risk factors may increase the risk of lung cancer. Smoking and other exposure to tobacco smoke are the main cause of lung cancer, with an estimated 90% of cases among men and over 80% of cases in women worldwide attributable to tobacco use.¹⁷ Other established causes of lung cancer include environmental exposures such as asbestos, radon, heavy metals, etc. and previous lung disease such as tuberculosis, emphysema and chronic bronchitis (see Figure 4).¹⁸

^a Defined as the conditions with the highest burden in term of years of life lost before 75 years.



Figure 4 – Common risk factors of lung cancer



Source: European Society for Medical Oncology (ESMO), 2019¹⁹

According to the Health Interview Survey (HIS) in 2018, 19% of Belgians aged 15 years or more were active smokers, 15% daily smokers, and 4% occasional smokers. The percentage of the population aged 15 years and over that currently smokes decreased from 28.5% in 2001 to 19.4% in 2018. The average amount of daily smoked cigarettes decreased from 17 in 2004 to 15 in 2018. In 2018, 4.7% of the smokers were categorized as heavy smokers, smoking at least 20 cigarettes per day.⁴

Based on the known risk factors for lung cancer, several approaches exist to identify high-risk individuals for whom lung cancer screening is considered most effective.²⁰ As smoking exposure accounts for the majority of lung cancers, many of the lung cancer screening studies focused on individuals with long-term smoking histories to define high-risk namely age, pack-year smoking history, and/or years since quit smoking. Another approach has been to develop multivariable models that estimate lung cancer risk over a

specified period and define a risk threshold to determine eligibility. Several of these risk prediction models for lung cancer incorporate risk factors such as family history of lung cancer, asbestos exposure, and chronic obstructive pulmonary disease (COPD).²¹



2.2. Cancer screening

2.2.1. Principles of screening

Screening is defined by the WHO as “the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population.”²² Within a cancer screening program, it is the aim to find a malignant tumour at an early stage when the disease is still curable and that way, to improve survival.

Population-based screening is a complex undertaking and various aspects should be considered before its implementation. The screening principles that were originally developed by Wilson and Jungner in 1968 often represent a major reference when making a screening decision.²³ These principles were recently updated by Dobrow et al. leading to 12 consolidated principles each aligned with three overarching domains: disease/condition, test/intervention or program/system principles (Table 1).²⁴ The revised principles have an increased focus on infrastructure requirements and resource or system capacity and program and performance management.²⁴

The first principles refer to the disease and test characteristics. The disease should have a sufficiently long period before symptoms occur so that a screening programme can be successful in identifying the disease earlier and the disease should still be treatable at that stage. Treatment for screen-detected disease should hence be available and significantly improve prognosis, compared to the prognosis of disease that is treated only after symptoms occur.

Other principles focus on organisational, health economic and ethical aspects of screening. Implementation of a screening programme should be cost-effective and be feasible in terms of resources, without negatively impacting other important activities within the health care system, for example no waiting lists for colonoscopy should be created due to screening, so that people with symptoms or signs can be helped without delay.²⁵ Each step in the screening process, starting with the identification of the target population, should be well thought off and accurately organised, with a quality assurance and monitoring system in place.

**Table 1 – Revised Screening principles by Dobrow et al.**

Summary of consolidated screening principles	
Disease or condition principles	1 Epidemiology of the disease or condition The epidemiology of the disease or condition should be adequately understood, and the disease or condition should be an important health problem (e.g., high or increasing incidence or prevalence, or causes substantial morbidity or mortality).
	2 Natural history of disease or condition The natural history of the disease or condition should be adequately understood, the disease or condition is well-defined, and there should be a detectable preclinical phase.
	3 Target population for screening The target population for screening should be clearly defined (e.g., with an appropriate target age range), identifiable and able to be reached.
Test or intervention principles	4 Screening test performance characteristics Screening test performance characteristics should be appropriate for the purpose, with all key components specific to the test (rather than the screening program) being accurate (e.g., in terms of sensitivity, specificity and positive predictive value) and reliable or reproducible. The test should be acceptable to the target population, and it should be possible to perform or administer it safely, affordably and efficiently.
	5 Interpretation of screening test results Screening test results should be clearly interpretable and determinate (e.g., with known distribution of test values and well-defined and agreed cut-off points) to allow identification of the screening participants who should (and should not) be offered diagnostic testing and other postscreening care.
	6 Postscreening test options There should be an agreed-on course of action for screening participants with positive screening test results that involves diagnostic testing, treatment or intervention, and follow-up care that will modify the natural history and clinical pathway for the disease or condition; that is available, accessible and acceptable to those affected; and that results in improved outcomes (e.g., increased functioning or quality of life, decreased cause-specific mortality). The burden of testing on all participants should be understood and acceptable, and the effect of false positive and false negative tests should be minimal.
Program or system principles	7 Screening program infrastructure There should be adequate existing infrastructure (e.g. financial resources, health human resources, information technology, facilities, equipment and test technology), or a clear plan to develop adequate infrastructure, that is appropriate to the setting to allow for timely access to all components of the screening program*
	8 Screening program coordination and integration All components of the screening program* should be coordinated and, where possible, integrated with the broader health care system (including a formal system to inform, counsel, refer and manage the treatment of screening participants) to optimize care continuity and ensure no screening participant is neglected.
	9 Screening program acceptability and ethics



Summary of consolidated screening principles

All components of the screening program* should be clinically, socially and ethically acceptable to screening participants, health professionals and society, and there should be effective methods for providing screening participants with informed choice, promoting their autonomy and protecting their rights.

10 Screening program benefits and harms

The expected range and magnitude of benefits (e.g., increased functioning or quality of life, decreased cause-specific mortality) and harms (e.g., overdiagnosis and overtreatment) for screening participants and society should be clearly defined and acceptable and supported by existing high-quality scientific evidence (of addressed by ongoing studies) that indicates that the overall benefit of the screening program outweighs its potential harms.

11 Economic evaluation of screening program

An economic evaluation (e.g. cost-effectiveness analysis, cost-benefit analysis and cost-utility analysis) of the screening program, using a health system or societal perspective, should be conducted (or clear plan to conduct an economic evaluation) to assess the full costs and effects of implementing, operating and sustaining the screening program while clearly considering the opportunity costs and effects of allocating resources to other potential nonscreening alternatives (e.g. primary prevention, improved treatments and other clinical services) for managing the disease of condition.

12 Screening program quality and performance management

The screening program should have clear goals or objectives that are explicitly linked to program planning, monitoring, evaluating and reporting activities, with dedicated information systems and funding, to ensure ongoing quality control and achievement of performance targets.

**Components of a screening program include recruitment, testing, information access, diagnosis, referral, treatment, follow-up, patient education and support, staff training and program management and evaluation.*

Source: Dobrow et al., 2018²⁴

2.2.2. Possible outcomes from screening

Possible results of a screening test: benefits and harms

A test that was performed with screening purposes can be 'positive' (signs of possible disease detected) or 'negative' (no signs of the disease detected). Both positive and negative results can be correct or incorrect and the final result of participating in a screening programme can be beneficial or can be harmful as summarised below (Figure 5). The majority of people will have no disease and have a negative test (**true negative**). The screening programme will only have a minor effect on them: the discomfort of undergoing the test and the short period of fear while awaiting the results. If the screening test consists of a yearly or 2-yearly X-ray or CT-scan, the

radiation dose and the associated risks are however an additional disadvantage to consider.

Nevertheless, some people with no disease will have some signs of possible disease or unclear findings (**false positive**). They will experience more harms from the screening programme. There will be fear and reduced quality of life by the news that they might have cancer and the discomfort of the additional tests, such as biopsies and repeated follow-up scans. The psychological consequences of a false positive result of a screening test may last for a long time.^{26, 27} Similar consequences can be experienced by people for whom the results of the test are 'inconclusive', and follow-up tests are needed.²⁸ Inconclusive results can also be considered as false positive results, as no reassurance is obtained.



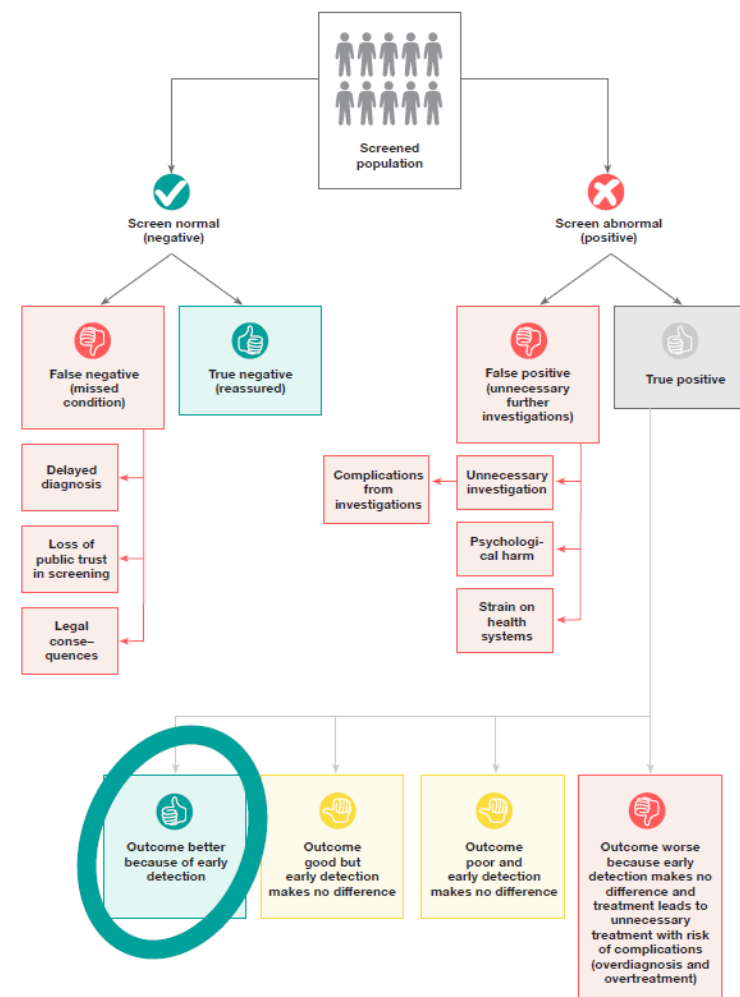
Also, people who have the disease can have incorrect test results; a screening test can miss the presence of disease (**false negative**). These people will not benefit from the screening programme and may even be harmed because of the false reassurance by the screening test, which may result in people not seeking medical advice for potential symptoms that occur.

A screening test can also reveal abnormal findings not related to the disease screened for but lead to further testing and possibly treatment. These so called **incidental findings** can be beneficial or harmful for the health of the screened person: as for the target disease of the screening test, early detection can prevent poor outcome but in other cases the additional testing may not lead to a meaningful diagnosis or the detected pathology may be harmless and be treated unnecessarily.²⁹

In a well-designed screening programme, however, the majority of people who have asymptomatic disease will have their disease detected by the screening programme (**true positive**), allowing them to start treatment timely and improve their prognosis. Another possible advantage is that treatment of the tumour can be less invasive, have fewer side effects and is associated with a better quality of life. These are the people who truly benefit from a screening programme.

For a screening programme to be effective, possible benefits and risks need to be well balanced (Figure 6).

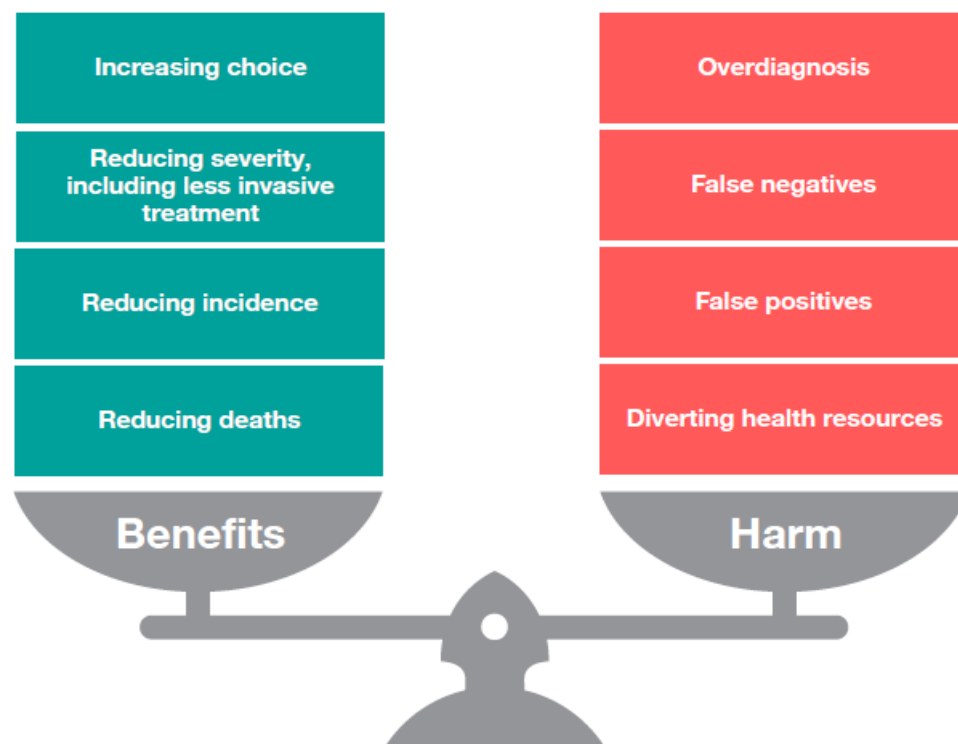
Figure 5 – Possible results of a screening test



Source: World Health Organization (WHO) - Screening programmes: a short guide, 2020⁹



Figure 6 – Balancing benefits and harms of screening



Source: World Health Organization (WHO) - *Screening programmes: a short guide*, 2020⁹



2.2.3. *Outcomes to assess the effectiveness of a screening programme*

Cancer stage, survival and mortality

Outcomes to evaluate a screening programme need to be well chosen. Based on how cancer screening works, an initial rise in the incidence of early-stage cancer is expected at the start of a screening programme, followed by a decrease in advanced-stage cancer over time. The decrease in the incidence of incurable cancer should then result in a decline of cancer-related death.

Incidence trends of advanced cancer have indeed been suggested as an appropriate measure to assess the effect of a cancer screening programme, as it has the advantage of being independent of treatment.^{30, 31} An increase in the proportion of early-stage cancer is a less reliable indicator for the effectiveness of screening, as this may be explained at least partly by overdiagnosis (see further).

For the same reason (overdiagnosis, but also lead-time bias), evolution of overall survival of cancer patients is not an appropriate parameter to assess the effectiveness of a screening programme. By the addition of cancers with a very good prognosis due to overdiagnosis, the average survival of that group cancer patients will appear to have improved without actually decreasing the absolute number of patients with a poor prognosis who die from their cancer. The aim of a screening programme, reducing the number of people dying from cancer, is better reflected in the age-standardized cancer-specific mortality in the population.

Cancer-specific versus overall mortality

In randomised controlled trials, cancer-specific mortality is often considered the most important primary outcome as the aim of screening is to prevent premature death caused by cancer.³² The focus on disease-specific survival has however been questioned. Cancer specific mortality relies on the identification of the cause of death, which has been shown to be complex and often biased. In addition, cancer-specific mortality does not take into account deaths related to the screening procedure (e.g; mortality due to

complications after surgery or colonoscopy). If only few patients with a certain type of cancer die due to their cancer, screening can only have a limited impact on actual survival and improvement in cancer-specific mortality may give a too optimistic image of the impact of a screening programme.³³ Hence, overall survival taking into account all screened patients has been put forward as a more important outcome to be put in the balance against the side effects and costs of a screening programme. Overall survival of all patients screened is the only outcome that provides an answer to the question whether a screening programme saves lives.³⁴

Another argument that often is brought forward to prefer cancer-specific mortality over overall mortality as the primary outcome of screening trials, is the needed sample size. Because the deaths due to cancer are only a subset of all-cause deaths, required sample size for all-cause mortality will be larger, rendering trials not feasible. However, it is important to assess the effect of a screening programme on all-cause mortality as the final impact will be a balance of prevented deaths by early detection and deaths caused by harms of the screening programme. Even if no statistically significant changes in all-cause mortality are noted, the direction and the absolute number of change in all-cause mortality compared to the changes in cancer-specific deaths can provide useful information on the balance between benefit and harms of a screening programme.³³ Moreover, meta-analysis of multiple trials reporting all-cause mortality may provide an effect estimate with sufficient statistical power.

Quality of life and psychological distress

Assessing the impact of a screening programme on quality of life is a complex undertaking, as all patients who take part in the screening programme have to be taken into consideration, or even all patients who are invited.

The aim of many screening programmes is not only to prolong survival, but also to improve quality of life by avoiding burdensome treatment for advanced stage cancer, which is often associated with many side effects that may affect patients in the long term. However, one has to be careful to consider all people with screen-detected cancer as benefitting in terms of quality of life. The proportion of patients that is confronted with overdiagnosis



are unnecessary labeled as cancer patients and undergo unnecessary treatment, both with an important negative impact on quality of life. In addition, as described above, a substantial proportion of patients will not benefit from screening, but may suffer from adverse consequences, such as discomfort related to the test (e.g., pain) or more severe morbidity such as bowel perforation after colonoscopy. This also includes the anxiety and stress when waiting for the test result or more importantly, the distress related to false positive (or intermediate) results. Although often modest, these harmful effects on the quality of life should not be overlooked as it concerns a lot of people and consequences may remain for a long duration.²⁷ To properly evaluate the psychological distress that can be provoked by screening, longitudinal measurements with questionnaires that are sufficiently responsive also to more subtle reactions are needed.³⁵ The longitudinal measurements should cover all the different steps in the screening process, such as the screening test itself, receipt of a positive or false positive result (including indeterminate results), the work-up after an

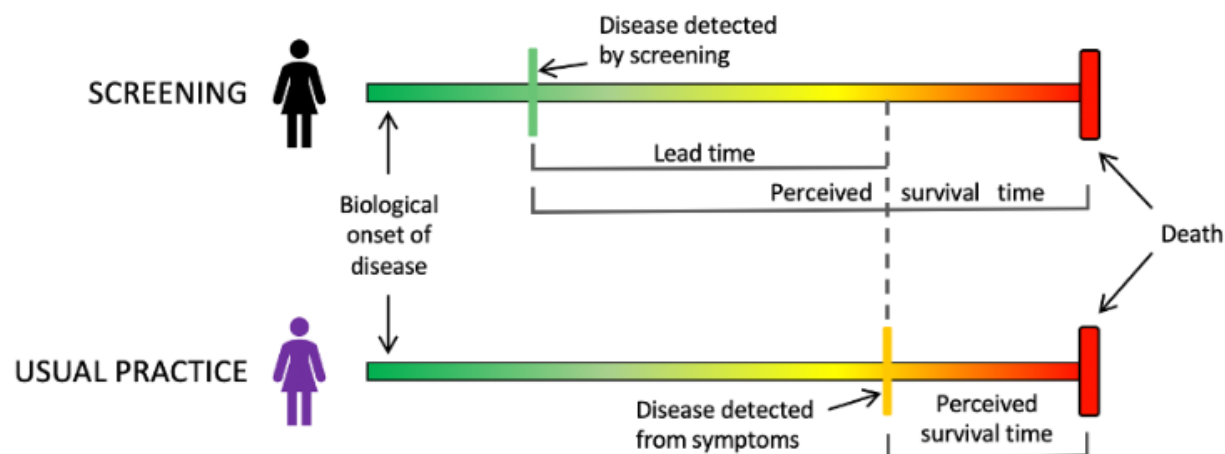
abnormal test result, receiving a diagnosis etc.³⁵ Even deciding whether or not to participate after having received an invitation can have psychological consequences, as people can feel anticipated regret when they would not participate and later be diagnosed with lung cancer.³⁶

2.2.4. Biases and caveats/pitfalls

When looking at the results of a screening programme, several biases may lead to a falsely optimistic image of the benefits.

Lead time bias for example, refers to the bias that occurs when the survival time of people diagnosed from screening is compared with the survival time of people whose disease is detected after symptoms have developed. Survival time of people diagnosed from screening will appear longer due to the early detection, even if the earlier detection has no effect on the course of the disease or the actual time of death.³⁷

Figure 7 – Lead time bias

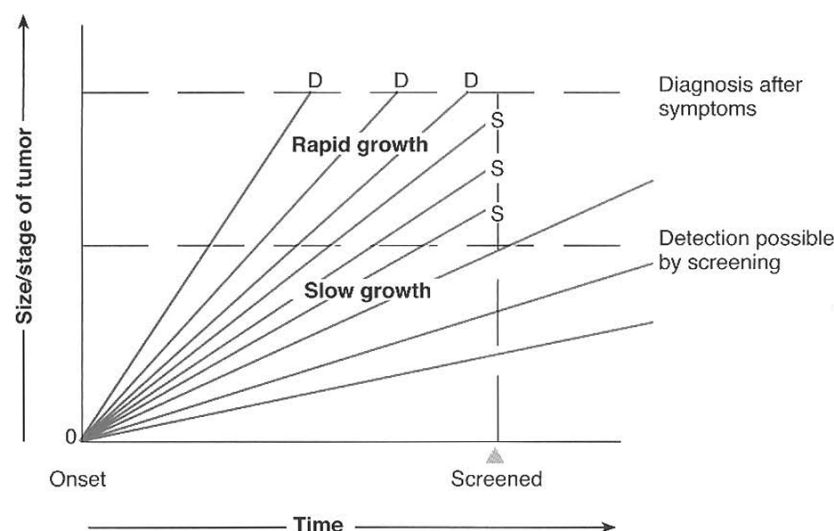


Source: Catalogue of Bias Collaboration, 2021³⁷



Length-time bias (see Figure 8) concerns the overestimation of survival benefit of screening, due to the relative excess of cases that are slowly progressing detected by screening, while fast-progressing cases are more often detected after giving symptoms.³⁸

Figure 8 – Relationship between length-time bias and speed of tumour growth



Abbreviations: D = diagnosis after symptoms; S = detection after screening.

Source: Fletcher et al., 2005³⁹

Volunteer bias or screening bias is a form of selection bias. It occurs because people who participate in screening programs tend to be healthier than those who do not volunteer or do not comply, with lower rates of mortality from all causes. An observed mortality difference may thus be due to a difference in population rather than the effect of screening.³⁸

Overdiagnosis

Another important caveat of screening is **overdiagnosis**. Overdiagnosis is the detection of cancers that would never have been found or never would have caused harm, were it not for the screening test.^{9, 40} Overdiagnosis is an important possible harm from screening, as people are unnecessarily labeled as cancer patients and receive unnecessary treatment (overtreatment), with all the detrimental effects on quality of life due to anxiety, side effects, financial issues, etc.

Although counter-intuitive, it is important to understand overdiagnosis. Three underlying reasons why tumours are overdiagnosed have been identified: malignant disease that would regress spontaneously if left alone, asymptomatic disease that does not progress or progress too slowly to be harmful during the lifetime of a patient, and asymptomatic disease that would progress and become life threatening during a lifetime of typical length but death occurs when patients die of other competing causes other than the screen-detected cancer.⁴¹

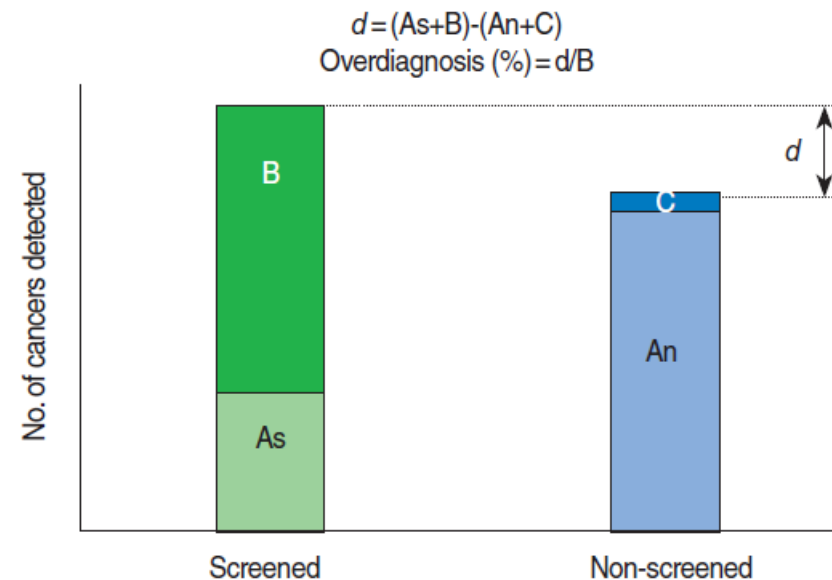
In clinical practice, overdiagnosed cancers cannot be distinguished from other tumours at the individual level, which makes it impossible to directly measure the degree of overdiagnosis in a screening programme. As a consequence, everyone who has a cancerous tumour diagnosed through a screening programme is offered treatment.⁹

When introducing a screening programme, an increase in the incidence of cancer is expected, as a proportion of cancers will be diagnosed earlier. This increase should normally be followed by a 'drop' in the number of cancer diagnoses when screening is stopped, by a reduced number of cancers in an advanced stage that were already diagnosed earlier through screening, called drop phenomenon. Afterwards, the incidence rate returns to the pre-screening level. In the absence of overdiagnosis, the overall number of tumours diagnosed over time would not increase. A first indication of overdiagnosis can be an increase of early-stage cancer without a decrease in the number advanced-stage cancers to the same degree.

Moreover, several research methods exist to estimate overdiagnosis from cancer screening. Two main approaches are the excess incidence approach and the lead time approach. The excess incidence approach is based on a comparison of disease incidence with and without screening. The lead time approach is a less direct method that compares the lead time with the time to competing death (which both need to be estimated).⁴²

In both approaches, it is important to correctly estimate the incidence in the absence of screening over time and two factors are of utmost importance to correctly do that. Firstly, it is important to include sufficient years of follow-up, at least covering the lead time of the type of cancer under study. The time that tumours need to become clinically apparent needs to be covered. Hence, estimates of overdiagnosis should be interpreted in view of the duration of follow-up. Secondly, another caveat when comparing incidence rates in randomised trials is the occurrence of contamination. If people in the non-screening arm of the trial take up screening anyway, it could lead to underestimation of the rate of overdiagnosis. Studies including sufficiently long follow-up and without contamination are thus to be preferred.⁴²

Figure 9 – Extent of overdiagnosis in a randomised trial



As: clinically detected cancers in the screened group; An: clinically detected cancers in the non-screened group; B: screen-detected cancers in the screened group; C: catch-up cancers of post-screening periods in the non-screened group; d: extra cancers

Source: Bae et al., 2015⁴⁰

2.2.5. Randomised controlled trials on screening

Randomised controlled trials (RCT) can vastly overcome these biases.

By taking the time of randomisation as starting point for survival time rather than the time of diagnosis, lead time bias is avoided. By including all patients in the analysis length-time bias and bias due to overdiagnosis are averted. RCTs are therefore the preferred method to assess the benefits and harms of a screening programme.⁴³



3. SYSTEMATIC REVIEW OF CLINICAL EFFECTIVENESS AND SAFETY OF LUNG CANCER SCREENING

3.1. Methods

3.1.1. Research questions

The aim of this chapter is to provide the evidence on the clinical effectiveness and harms of lung cancer screening using low-dose computed tomography (LDCT) in an adult high-risk population. A systematic literature search was performed to answer the following research questions:

- What is the clinical effectiveness of LDCT screening in an adult high-risk population, compared to other screening strategies or no screening?
- What are the harms associated with LDCT screening in an adult high-risk population, compared to other screening strategies or no screening?

3.1.2. Search strategy

The systematic literature review was performed in two stages. In an initial phase, we searched for systematic reviews and meta-analyses reporting benefit and harm results of randomised controlled trials (RCTs) of lung cancer screening using LDCT. Secondly, we performed a systematic literature search for RCTs for the time period not covered by an up-to-date systematic review of good quality.

3.1.2.1. Search for systematic reviews

To identify relevant published systematic reviews, we conducted systematic searches of literature in the following databases:

- Cochrane Database of systematic reviews (<http://www.cochrane.org>)
- Medline (<https://ovidsp.ovid.com/ovidweb.cgi>)

- Embase (<https://www.embase.com/>)

In addition, existing Health Technology Assessments (HTAs) related to lung cancer screening were searched using the websites of HTA institutes, which are members of the International Network of Agencies for Health Technology Assessment (INAHTA). An overview of the included HTA institutes can be consulted in Appendix 1 - Table 94.

We searched for systematic reviews and meta-analyses published from 2020 onwards, as the main results of the Belgian-Netherlands lung cancer screening study (NELSON) were published in that year.¹⁰ Only reviews which report on RCTs were included in the assessment, as they provide the most reliable evidence of benefits and harms of different screening strategies. Reviews including studies that compare LDCT screening to other screening strategies such as chest x-ray (CXR) were also taken into account, although this does not reflect the current standard of care in Belgium (i.e., no screening). We justify the inclusion of these reviews as follows: CXR screening has not shown to reduce lung cancer-related mortality,⁴⁴ hence there is reason to assume comparability of no screening and screening using CXR. In studies with CXR screening as comparator, the effect of LDCT screening may have been diluted at most, enforcing a positive result of the study. Moreover, studies comparing different screening strategies may provide additional information regarding harms of LDCT screening. Finally, sensitivity analyses allow excluding studies with CXR screening as comparator to reflect current Belgian standard of care, if deemed appropriate for certain outcomes.

We used a combination of MeSH terms and free text words. The detail of each strategy with date of the search and number of articles found is provided in Appendix 2. Study selection was initially performed by one researcher in two phases. Phase one consisted of screening the titles and abstracts of the retrieved studies and excluding studies for which it was obvious that they did not fulfil the inclusion criteria. In phase two, of the remaining studies, the full text was screened. An overview of the pre-defined inclusion criteria that were used in this phase of the systematic literature review is provided in Table 2, based on the PICO (Participants–Interventions–Comparator–Outcomes) framework. A second researcher reviewed this search strategy.

**Table 2 – Inclusion criteria for systematic literature review**

Description	Inclusion
Population	Adults (age ≥ 18 years) without lung cancer at elevated risk of lung cancer (as defined by author)
Intervention	Screening with LDCT
Comparator	No screening or alternative screening methods
Outcomes	All-cause mortality Lung cancer-related mortality Harms resulting from screening, e.g., (consequences of false positive screening results, overdiagnosis (not exhaustive) Health-related quality of life Cancer stage at diagnosis and stage shift
Study design	Systematic reviews with or without meta-analysis with the following characteristics: • Clearly defined in- and exclusion criteria • Reporting on RCTs • Characteristics of included studies reported • Critical appraisal of included studies
Period	Search date from 2020 onwards, to include results of NELSON
Language	No language restriction was imposed

3.1.2.2. Update of systematic review and ongoing trials

An update systematic review was performed of a previous good-quality systematic review which met the beforementioned inclusion criteria, thereby excluding all studies already selected in the previous systematic review.

A search for ongoing RCTs with mortality outcomes was done in the available trial registers in the the National Library of Medicine (NLM) at the National Institutes of Health (NIH) Trial Registry (clinicaltrials.gov), the EU Clinical Trials Register (clinicaltrialsregister.eu), the International Standard Randomised Controlled Trial Number Registry (ISRCTN) (isrctn.com), and the International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int).

Finally, ongoing trials at the time of publication of the systematic review were assessed separately to evaluate if results have been published in the meantime.

3.1.2.3. AMSTAR 2 and GRADE

The methodological quality of systematic reviews was assessed by one researcher using the AMSTAR 2 instrument^{b,45}

To evaluate the level of evidence identified in the systematic reviews, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used as suggested in the Cochrane Handbook for Systematic Reviews of Interventions.⁴⁶

GRADE assessments of certainty are determined through consideration of five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias, applied to the body of evidence for each individual outcome. Following the GRADE methodology (Table 3), the quality of evidence was classified into four categories: high, moderate, low, and very low. The GRADE level of evidence expresses the confidence that can be put in the results of a meta-analysis (Table 4). If GRADE assessments were available in good-quality systematic reviews, the assessment were not repeated but verified and accepted.

^b http://amstar.ca/Amstar_Checklist.php


Table 3 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias	1. Large effect	High (⊕⊕⊕⊕)
Observational studies	Low	2. Inconsistency	2. Dose-response	Moderate (⊕⊕⊕⊖)
		3. Indirectness	3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	Low (⊕⊕⊖⊖)
		4. Imprecision		Very low (⊕⊖⊖⊖)
		5. Publication bias		

Source: Guyatt et al. (2011)⁴⁷

Table 4 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem et al. (2011)⁴⁸



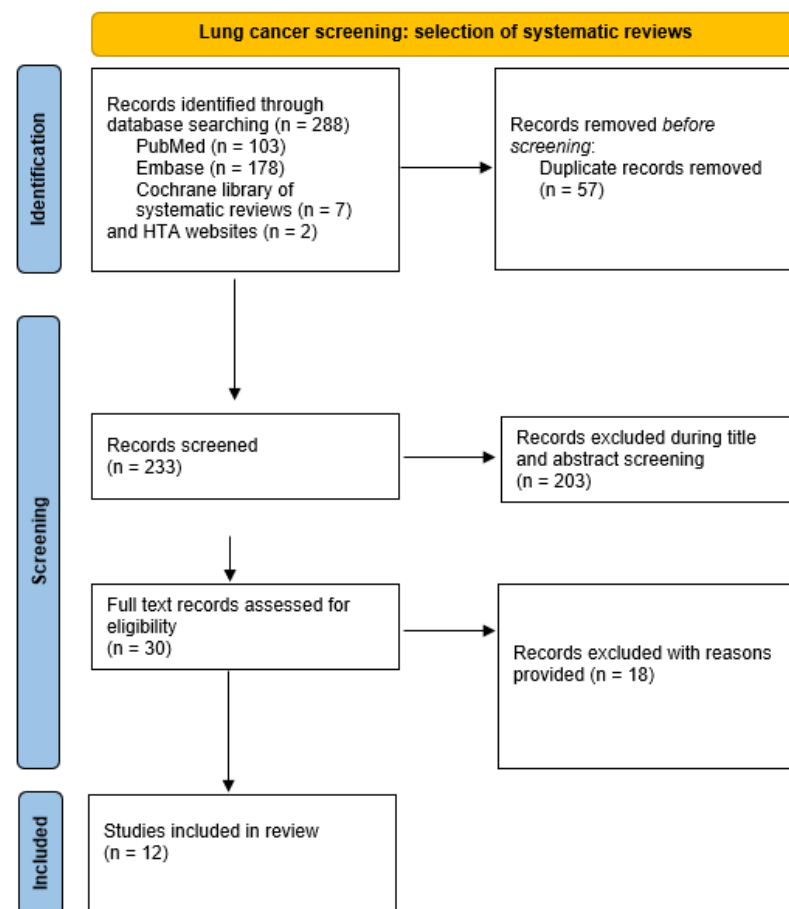
3.2. Results

3.2.1. Quantity of evidence

3.2.1.1. Search for systematic reviews

The search for systematic reviews in the Cochrane library of systematic reviews, in PubMed and in Embase, yielded 288 records (Figure 10). Another two HTA reports were identified. After de-duplication, 233 remaining records were screened based on title and abstract, of which 203 were excluded. In total, 30 full text reports/articles were assessed for eligibility. Based on full text evaluation, 18 reviews were excluded (see Table 100 in Appendix 2 for an overview of these studies and the reason for exclusion). Twelve systematic reviews with or without meta-analysis met our inclusion criteria.

Figure 10 – Selection of relevant systematic reviews (PRISMA flow chart)



HTA: health technology assessment; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses



The overall outcome of the critical appraisal process for each of the 12 systematic reviews and meta-analyses is provided in Table 101 in the Appendix. After methodological quality assessment, three recent, high-quality reviews were identified and included in the effectiveness and harms overview:

- EUnetHTA assessments on lung cancer screening in risk groups⁴⁹
- United States Preventive Services Taskforce (USPTF) evidence review of lung cancer screening⁵⁰
- Cochrane review on the impact of LDCT screening on lung cancer-related mortality⁵¹

These reviews included RCTs of lung cancer screening using LDCT and reporting mortality or harm outcomes in adult patients at high risk of developing lung cancer. A total of 11 RCTs were described by the systematic reviews, and all of them were reported by Bonney et al. EUnetHTA and Jonas et al. also included non-randomised studies to evaluate participation rates and harms of screening. Both in EUnetHTA and Bonney et al., a meta-analysis of the included RCTs was performed whilst Jonas et al. refrained from conducting a meta-analysis because of substantial clinical and methodological heterogeneity between the RCTs. Table 5 provides an overview of the systematic reviews with included RCTs and reported outcomes.



Table 5 – Overview of systematic reviews

	Systematic reviews (date of publication)		
	EUnetHTA report (2020) ⁴⁹	USPTF report (2021) ⁵⁰	Cochrane review (2022) ⁵¹
Design	Systematic review and meta-analysis	Systematic review	Systematic review and meta-analysis
Searched databases	CENTRAL, MEDLINE, Embase, HTA database	MEDLINE, the Cochrane Library, and trial registries	CENTRAL, MEDLINE, Embase, Cochrane Lung Cancer Group Trial Register, trial registries
Search range	2013 to June 2020	Inception to May 2019, with surveillance of literature until March 2020	Inception to 31 July 2021
Included RCTs	NLST, NELSON, LSS, DANTE, DLCST, ITALUNG, LUSI, MILD, UKLS (n=9)	NLST, NELSON, LSS, DANTE, DLCST, ITALUNG, LUSI, MILD, UKLS (n=9)	NLST, NELSON, LSS, DEPISCAN, MILD, DANTE, DLCST, ITALUNG, LUSI, UKLS, LaRocca (n = 11)
Target population	Adults ≥18 years at elevated risk of lung cancer	Asymptomatic adults ≥18 years	Asymptomatic adults ≥18 years
Comparator	- No screening - CXR screening	- No screening - CXR screening	- No screening - Any other screening
Outcomes	Mortality (lung cancer-related and all-cause), adverse events, harms of false negative and false positive screens, overdiagnosis, HRQoL	Mortality (lung cancer-related and all-cause), stage at diagnosis, lung cancer incidence, psychosocial harms, overdiagnosis, smoking cessation, incidental findings	Mortality (lung cancer-related and all-cause), lung cancer incidence, cancer stage at diagnosis, false positive, false negative and recall rates, smoking cessation, HRQoL, histology, other outcomes
Comments	UKLS: ongoing study, only preliminary findings (accuracy, FP rates), but no mortality outcomes reported	UKLS: ongoing study, only preliminary findings (accuracy, FP rates), but no mortality outcomes reported	UKLS: long-term data included

Abbreviations: CXR = chest x-ray; DANTE = Italian Detection And screening of early lung cancer by Novel imaging TEchnology trial; DEPISCAN = French randomized pilot trial of lung cancer screening; DLCST = Danish Lung Cancer Screening Trial; FP = false positive; HRQoL = Health-related quality of life; ITALUNG = Italian Lung Cancer Screening trial; LaRocca = North American Jewish Hospital Lung Cancer Screening and Early Detection Study; LSS = US Lung Screening Study; LUSI = German Lung Cancer Screening Intervention; MILD = Multicentric Italian Lung Detection trial; NELSON = Dutch-Belgian Nederlands-Leuven Longkanker Screenings Onderzoek trial; NLST = US National Lung Screening Trial; UKLS = UK Lung Cancer Screening trial.



Among 11 included RCTs, three trials were conducted in the USA and the remaining trials were based in Europe. Overall, 94 445 people were included across the trials, ranging between 53 456 participants in the NLST trial and 765 participants randomised in the DEPISCAN trial. All trials had a smoking history requirement of at least 20 pack years as part of the inclusion criteria, except the UKLS trial, which used a lung cancer risk calculator. Nine out of eleven trials had a lower age limit of 50 years or older. Most of the participants were male, no included trial reported equal representation of male and female participants, and the DANTE trial excluded all women from the trial. Seven trials had additional fitness requirements, including fitness

for surgery for entry into the trial. LDCT is the intervention in all trials, but frequency and duration of scans varied between trials. Six of the eleven trials used no screening in the comparator arm, while four used annual CXR screening as comparator and one trial used a baseline CXR screening in the comparison arm. Included trials used different size and volumetric assessment to determine the significance of pulmonary nodules. Follow-up varied from 5 up to 10 years post-randomisation. Table 6 shows the characteristics of each of the RCTs included by one or more of the included systematic reviews. Harms outcomes will be presented in separate tables to allow a clear presentation.

Table 6 – Characteristics of included clinical trials of lung cancer screening with LDCT

Trial Year of publication Location	Control	N part. N contr.	Population - Age - Sex (% male) - Pack-years; years since quitting	Screening intervals (years)	Threshold for positive nodule result	Total median follow-up	Benefit outcomes (RR) - LC mortality - All-cause mortality
NLST⁵² 2011 USA	CXR	26 723 26 723	- 55 - 74y - 59% male - ≥30; ≤15y	0,1,2	≥4 mm maximum diameter	7y	0.80 [0.70-0.92] 0.94 [0.88-1.00]
NELSON¹⁰ 2020 Belgium- Netherlands	Obs.	7900 7892	- 50 - 74y - 83% male - >15 cig/d for >25y or >10 cig/d for >30y; ≤10y	0,1,3,5,5	Volumetric	10y	0.75 [0.62-0.90] 0.98 [0.90-1.07]
LSS⁵³ 2005 USA	CXR	1660 1658	- 55 – 74y - 58% male - ≥30; ≤10y	0,1	≥3 mm maximum diameter	5y	1.23 [0.74-2.05] 1.20 [0.94-1.52]
DEPISCAN⁵⁴ 2007 France	CXR	385 380	- 50 - 75y - 71% male - >15 cig/d for >20y; ≤15y	0,1,2	Size >5mm	NR	NR
MILD⁵⁵ 2012	Obs.	2376 1723	- ≥50y - 68% male	0-6 (annual)	Volumetric	10y	0.73 [0.47-1.12] 0.94 [0.73-1.20]



Trial Year of publication Location	Control	N part. N contr.	Population - Age - Sex (% male) - Pack-years; years since quitting	Screening intervals (years)	Threshold for positive nodule result	Total median follow-up	Benefit outcomes (RR) - LC mortality - All-cause mortality
Italy			- ≥20; ≤10y	0,2,4,6,8 (biennial)			
DANTE⁵⁶	Baseline	1264	- 60 – 74y	0,1,2,3,4	>5 mm average diameter	8y	1.01 [0.70-1.44]
2015	CXR	1186	- 100% male				0.96 [0.79-1.16]
Italy			- ≥20y; ≤10y				
DLCST⁵⁷	Obs.	2052	- 50 – 70y	0,1,2,3,4	Volumetric	10y	0.65 [0.41-1.03]
2016		2052	- 56% male				1.01 [0.82-1.25]
Denmark			- ≥20y; ≤10y				
ITALUNG⁵⁸	Obs.	1613	- 55 – 69y	0,1,2,3	≥5 mm average diameter	9y	0.71 [0.48-1.04]
2017		1593	- 64% male				0.84 [0.69 -1.03]
Italy			- ≥20; ≤10y				
LUSI⁵⁹	Obs.	2029	- 50 - 69y	0,1,2,3,4	≥5 mm average diameter	9y	0.72 [0.45-1.16]
2020		2023	- 65% male				0.98 [0.79-1.22]
Germany			- >15 cig/d for >25y or >10 cig/d for >30y; ≤10y				
UKLS⁶⁰	Obs.	2028	- 50 – 75y	0	Volumetric	7y	0.65 [0.41-1.03]
2021		2027	- 75% male				0.92 [0.78-1.08]
UK			- LLP ≥ 4.5%				
LaRocca⁶¹	CXR	871 in total	- 40-74y	0,1,2,3,4	Size ≥5mm	NR	No mortality data
2002			- NR				
USA			- ≥30; ≤10y				

Abbreviations: RR = risk ratio; NR = not reported; CXR = chest x-ray; Obs = observation.



3.2.1.2. Update of systematic review and ongoing trials

Update of the Cochrane review

We performed an update of the literature search that was used in the Cochrane review,⁵¹ using the same search strategy but with date limits of 2021 until the 6th of July 2023. The flow of the references through the search process is presented in Figure 41.

Our search for primary studies published since the SR of Bonney et al. returned 32 publications, and 19 records were discarded after analysis of full text (Table 103). No additional randomised trials with published results were identified. Of the 13 remaining publications, 10 refer to trials included in the Cochrane review. Qian et al. provides a brief summary of outcome data of the Chinese AME Thoracic Surgery Collaborative Group Study as presented during the the 2022 World Conference on Lung Cancer.⁶² This trial was described in the Cochrane review as an ongoing trial. We contacted the corresponding author of this trial for more detailed results without response. Rong et al. described the baseline data of a Chinese community-based lung cancer screening trial among 900 participants.⁶³ Finally, Li et al. provided a systematic review to identify estimates of overdiagnosis from RCTs of LDCT screening, they did not identify trials different than the ones listed above.⁶⁴ An overview of included publications of the updated systematic review is provided in Table 102.

Search for ongoing trials

We did not identify other ongoing randomized controlled trials with mortality outcomes other than the ones reported in the Cochrane review namely, the Japanese JECS Study and the Chinese AME study.

It should be noted that several ongoing trials don't assess mortality outcomes, but focus on stage I and II lung cancer incidences as surrogates for evaluating the effectiveness of LDCT screening. Several of them are comparing different LDCT-based screening strategies, such as the RISP study, the SMILE study, and 4-IN THE LUNG RUN^c. Furthermore, many ongoing pilot screening studies and single-arm trials do not meet our inclusion criteria (e.g., the HANSE study is a prospective cohort study which aims to compare different selection criteria models and nodule management algorithms⁶⁵, the SUMMIT study is a prospective cohort study which aims to evaluate a multi-cancer early detection test and the performance of LDCT screening⁶⁶).

3.2.2. Quality of evidence

3.2.2.1. Systematic reviews

All three included systematic reviews nearly meet all the AMSTAR 2 criteria and therefore are deemed to be high-quality reviews. Bonney et al. did not specifically explain why only RCTs and no observational studies were considered. We did not retrieve all sources of funding for individual studies included in the review of EUnetHTA. Jonas et al. did not assess the likelihood of publication bias. We don't estimate these elements justify downgrading the quality of these systematic reviews. We refer to Table 7 for an overview of the quality assessment using the AMSTAR 2 instrument.

^c RISP: Early Diagnosis of Lung Cancer of the Italian Pulmonary Screening Network (RISP): Comparative Analysis for the Use of Low Dose Computed Tomography and Promotion of Primary Prevention Interventions in Subjects at High Risk for Lung Cancer (NCT05766046); SMILE: Screening and

Multiple Intervention on Lung Epidemics (SMILE) (NCT03654105); 4-IN THE LUNG RUN: towards INdividually tailored INVitations, screening INTERVALs, and INtegrated co-morbidity reducing strategies in lung cancer screening (NL9710 (Netherlands Trial Register)).


Table 7 – Quality appraisal of included systematic review, using the AMSTAR 2 instrument

Systematic review	1. PICO components	2. Protocol	3. Study design explanation	4. Comprehensive search strategy	5. Duplicate study selection	6. Duplicate data extraction	7. Details of excluded studies	8. Description of included studies	9. RoB assessment	10. Funding sources	11. Appropriate methods	12. Impact of RoB	13. RoB in discussion	14. Heterogeneity	15. Publication bias	16. Reports conflicts of interest
Bonney 2022 ⁵¹																
EUnetHTA 2020 ⁴⁹																
Jonas 2021 ⁵⁰											N/A	N/A				

Green color: yes; red color: no.

Abbreviations: N/A = not applicable.

3.2.2.2. Individual RCTs

Critical appraisal of included RCTs was provided in all three systematic reviews, using different critical appraisal tools. In the EUnetHTA report, risk of bias (RoB) was assessed according to the Cochrane RoB 1 tool, rating each domain of the tool as having 'low', 'high', or 'unclear' risk of bias. An overall RoB score was provided at study level for each RCT. For all the studies for which RoB at the study level was already classified as high RoB, they deemed a high RoB at the outcome level, so no further outcome-specific assessment was performed for these studies. Jonas et al. used a tool developed by the USPSTF to provide overall quality ratings of good, fair, or poor. Only studies rated as having good or fair quality were included, and no specific quality assessment at outcome level was provided. Bonney et al. also used the Cochrane RoB 1 tool for the quality assessment of included RCTs. They refrained from providing an overall quality score at study level but provided an extensive analysis of each RoB domain and summarised the results in a RoB graph.

In the EUnetHTA report, the RoB at study level was rated as low for four studies (DLCST, ITALUNG, LUSI and NELSON), and high for the remaining four studies (MILD, NLST, DANTE and LSS). The study authors judged unclear whether the randomisation sequence was adequately generated (MILD and NLST) or whether the allocation concealment was adequate (DANTE, MILD and NLST). For LSS, it was unclear whether reporting was independent of the results (such as lack of information on the planned endpoints). Significant differences in baseline characteristics between intervention and control group led to high RoB in MILD.

Jonas et al. considered most RCTs as fair, indicating they had generally comparable groups but with some questions remaining about the methodology, although with no fatal flaws. NLST was rated as good quality for the main trial outcomes, while post-trial follow-up was rated as fair quality because outcomes were measured without a verification committee during post-trial years. Regarding the NELSON trial, risk of ascertainment bias (lack of death review panel in 30 per cent of lung cancer deaths) and lacking details on potential harms of screening were the main methodological

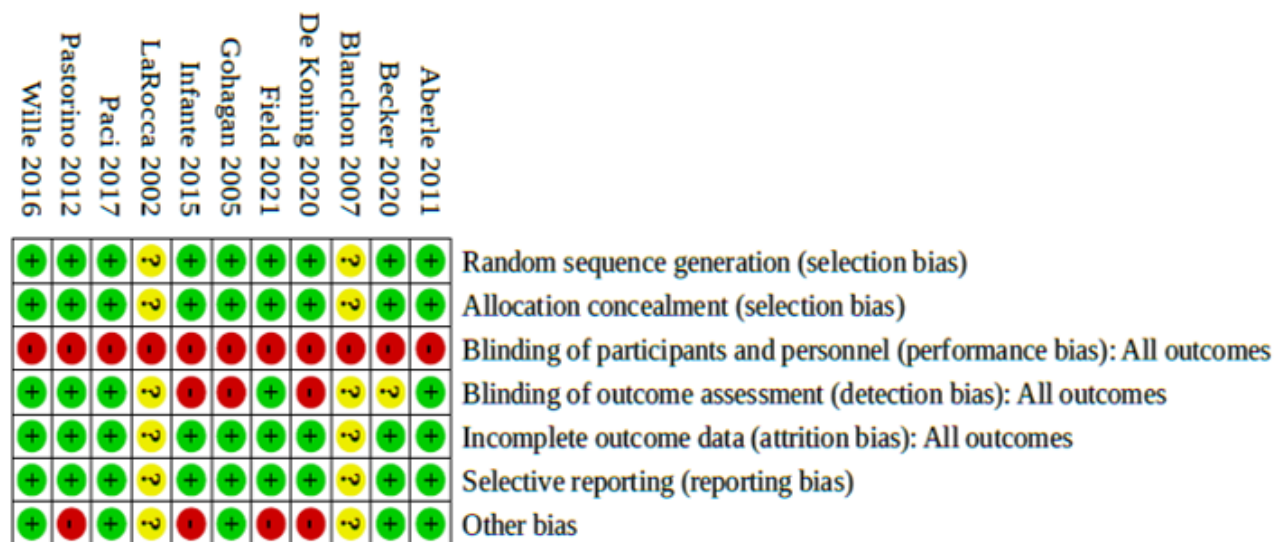


limitations. Jonas et al. didn't include the results of MILD in their systematic review, because of poor methodological quality. There are concerns about a high risk of selection bias, differential follow-up between groups, high risk of measurement bias, and inability to reach its planned sample size.

The DEPISCAN and LaRocca trial, which were only included in the Cochrane review, had insufficient information available to make a judgement across the different domains of possible bias and were therefore deemed at unclear risk of bias by Bonney et al. Three studies (NELSON, LSS and DANTE) were deemed at high risk of bias due to lack of blinding of the outcome assessment. LSS and DANTE did not blind outcome assessors, while NELSON unblinded assessors during trial follow-up. LSS only

assessed cause of death from death certificates (without the use of a review board). Four of the 11 trials were judged at high risk of other bias (NELSON, DANTE, MILD, UKLS). NELSON was judged at high risk of other bias because of changing the assessment of lung cancer deaths from a review board to death certificates during follow-up and adding a scan interval of 2.5 years after trial commencement. DANTE did not recruit women, and there was an unbalanced baseline between trial arms. MILD had unbalanced baseline characteristics between intervention and control arm, and the no-screening control group was added later when the trial had already started. A visualisation of the risk-of-bias assessment performed by Bonney et al. is shown in Figure 11.

Figure 11 – Risk of bias summary of individual LDCT trials, as judged by Bonney et al.



Source: Bonney et al. (2022)⁵¹

Aberle = NLST; Becker = LUSI; Blanchon = DEPISCAN; De Koning = NELSON; Field = UKLS; Gohagan = LSS; Infante = DANTE; Paci = ITALUNG; Pastorino = MILD; Wille = DLCST.



In general, the included trials were of fair quality and there was variable concordance between systematic reviews. Given the nature of the intervention, blinding of patients into their trial arm was impossible. However, objective outcomes such as mortality and false positive rate are less at risk of bias from lack of blinding. MILD was excluded for analysis in Jonas et al. for poor methodological quality, and the same concerns were raised in EUnetHTA (high overall RoB) and in Bonney et al. (high risk of other bias). Interestingly, EUnetHTA deemed NLST at high RoB at study level for unclear randomisation, whereas Jonas and Bonney et al. did not share this concern. Bonney et al. concluded that included trials were generally well-designed, although limited use of death panels to review lung cancer-related mortality may have influenced detection bias. Consequently, Bonney et al. preferred using planned and active follow-up data over unplanned extended follow-up in their analyses, given concerns regarding completeness of registry data during extended follow-up.

3.2.3. All-cause mortality

Of all included RCTs that report on all-cause mortality, only NLST observed a significant reduction in all-cause mortality for LDCT compared to CXR after 6.5 years of follow-up: incidence rate ratio (IRR) 0.93 (95% CI 0.88-0.99). As such, NLST is considered the only cancer screening trial targeting a single cancer type, which showed a significantly reduced all-cause mortality.⁶⁷ When considering RR instead of IRR^d, this reduction is not significant: RR 0.94 (95% CI 0.88-1.00) after 6.5 years of follow-up. The extended follow-up results (median 12.3 years) of NLST showed no statistically significant differences between groups: RR 0.98 (95% CI 0.95-1.01). Jonas et al. judged NELSON as the only other trial sufficiently powered to evaluate all-cause mortality and reported an IRR of 1.01 (95% CI 0.92-1.11) for LDCT in comparison to no screening. Other trials are considered underpowered to demonstrate a reduction in all-cause mortality.

As stated before, Jonas et al. refrained from conducting a meta-analysis because of substantial clinical and methodological heterogeneity between the RCTs.

The meta-analysis of EUnetHTA reported a non-significant reduction of 3 percent in all-cause mortality (95% CI 0.92-1.02) when pooling together studies at low and high RoB comparing LDCT screening to no screening or CXR screening (n = 8 studies, no heterogeneity between studies). For all RCTs, the data for the longest observation period were used (between 8 and 11 years since randomization). The analysis for comparison against no screening (n=6) does not contradict this result, and only considering three studies with low RoB also showed no statistically significant difference between the groups. The review authors conclude screening for lung cancer with LDCT results in little or no difference in overall mortality compared with no screening, based on high-quality evidence.

Bonney et al. included 8 RCTs for the meta-analysis of all-cause mortality using LDCT compared to no screening or CXR screening (NLST, NELSON, MILD, DANTE, DLCST, ITALUNG, LUSI, UKLS). Compared to the meta-analysis of EUnetHTA, they included data of the UKLS trial and excluded one trial (LSS) as the planned follow-up for this trial was only 2 years. Bonney et al. reported a significant reduction of 5% in all-cause mortality (RR 0.95 95% CI 0.91-0.99) with LDCT screening when combining trial data from all eight available trials using the latest planned follow-up time point for each trial (6 to 10 years after randomization, comparing to no screening or CXR screening, moderate-certainty evidence). To prevent one death from all-cause mortality, 210 people would need to be screened during this timeframe. When performing a sensitivity analysis using trials with low risk of bias (NLST, ITALUNG, DLCST), the analysis still favoured screening with LDCT (RR 0.94, 95% CI 0.89 to 0.99).

^d The incidence rate ratio (IRR) compares the **incidence rates** of events (death from any cause, per x person-years) in the screened and control group at any given point in time. The risk ratio (RR) divides the **cumulative incidence** of events in the screened group by the cumulative incidence in the control group.



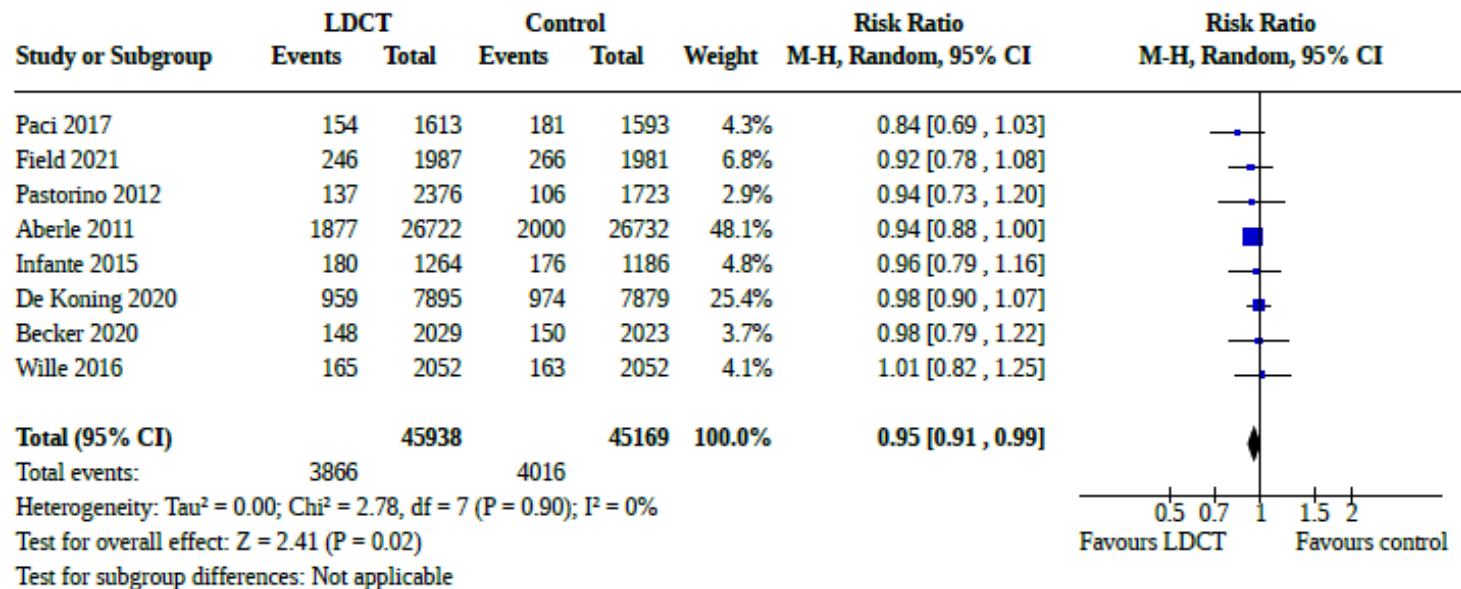
Discussion

Only NLST showed a significant reduction in all-cause mortality at the latest planned follow-up, although the statistical significance depends on the used measure (IRR versus RR) and extended follow-up results were no longer statistically significant. NELSON is the second largest trial and considered the only other trial sufficiently powered to demonstrate this outcome but did not show a reduction in all-cause mortality.

Both EUnetHTA and Bonney et al. performed meta-analysis of all-cause and lung cancer-related mortality, but there are some differences in approach between the two reviews. EUnetHTA used data from the longest observation

period, whereas Bonney et al. prioritized data from planned follow-up points over unplanned extended follow-up. They express concerns regarding completeness of extended follow-up data, which relied more on registry data than death panel data. This would especially be relevant for outcomes such as lung cancer-related mortality, whereas all-cause mortality is less likely to be influenced by detection bias. Finally, the mortality data of the UKLS trial were only included in Bonney et al, which is the most recent systematic review. Therefore we adopted this as the main result for lung cancer-related mortality in this report. A copy of the meta-analysis of Bonney et al. is provided in Figure 12.

Figure 12 – Meta-analysis of all-cause mortality in LDCT screening, using latest planned time points



Source: Bonney et al. (2022)⁵¹

Paci = ITALUNG; Field = UKLS; Pastorino = MILD; Aberle = NLST; Infante = DANTE; De Koning = NELSON; Becker = LUSI; Wille = DLCST.



Key points

In people at high risk of lung cancer based on smoking history, screening with low dose CT scan reduces overall mortality (RR 0.95, 95% CI 0.91 to 0.99, moderate-certainty evidence).

3.2.4. Lung cancer-related mortality

Only two RCTs have reported a reduction in lung-cancer related mortality using LDCT screening compared to no screening (NELSON) or CXR screening (NLST). The original publication of NLST reported a relative risk reduction in lung cancer mortality of 20 percent (RR 0.80, 95% CI 0.70-0.92) in three rounds of LDCT compared to CXR over 6.5 years of follow-up, which was the latest planned follow-up point. Analysis of extended follow-up data of NLST participants at 12.3 years after randomization found a relative risk reduction of 8 percent (RR 0.92, 95% CI, 0.85 to 1.00). NELSON reported a relative risk reduction in lung cancer mortality of 25 percent (RR 0.75, 95% CI 0.62-0.90) for four rounds of LDCT compared to no screening over 10 years of follow-up. Results of the other RCTs were imprecise and did not show statistically significant differences in lung cancer-related mortality between LDCT screened and control groups.

EUnetHTA reported a reduction in lung cancer-related mortality in the LDCT screened group compared to the control groups as a decrease in incidence rate ratio (IRR). For all studies, the data for the longest observation period were used. For their initial comparison of LDCT screening against no screening, combined analysis of studies with low and high RoB showed a statistically significant effect in favour of LDCT screening (IRR 0.81, 95% CI 0.72–0.91). The three studies with low RoB according to the authors (DLCST, ITALUNG, NELSON) showed no statistically significant difference

between the groups (IRR 0.80, 95% CI 0.60–1.06). The EUnetHTA authors conclude that screening for lung cancer with LDCT probably reduces lung cancer mortality compared with no screening, based on moderate-certainty evidence. When performing a sensitivity analysis after adding the two studies comparing LDCT to CXR screening (LSS, NLST), the results do not contradict the results for the comparison of LDCT screening to no screening (IRR 0.89, 95% CI 0.82–0.96).

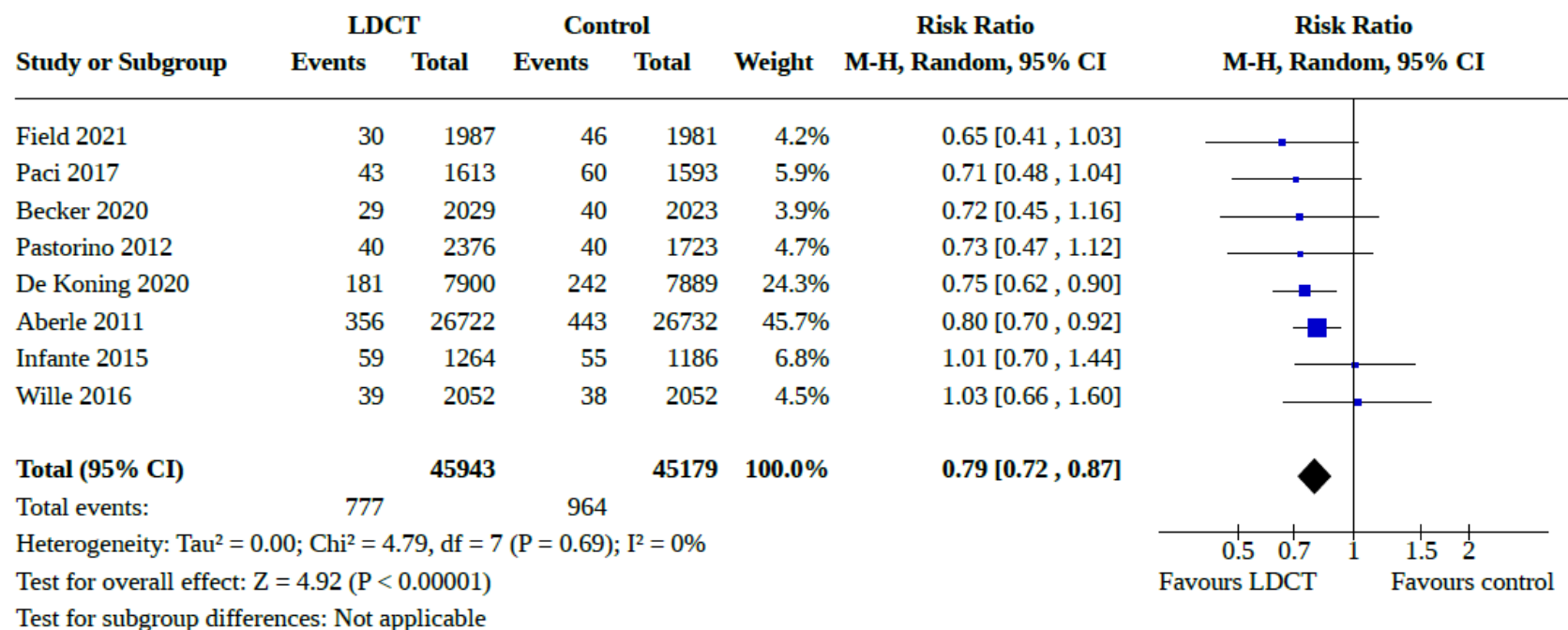
Bonney et al. included 8 RCTs for the meta-analysis of lung cancer-related mortality using LDCT compared to no screening or CXR screening (NLST, NELSON, MILD, DANTE, DLCST, ITALUNG, LUSI, UKLS). Their analysis showed a difference in lung cancer-related mortality favouring screening with LDCT, with a reduction in lung cancer-related mortality of 21 percent (RR 0.79, 95% CI 0.72-0.87, moderate-certainty evidence). When performing a sensitivity analysis including three trials with low risk of bias (NLST, ITALUNG, DLCST), the evidence still favoured screening, with a reduction in lung cancer-related mortality of 19 percent (RR 0.81, 95% CI 0.71 to 0.92, high-certainty evidence). The number needed to screen to prevent one additional lung cancer-related death was 296.

Discussion

The evidence presented in three included systematic reviews supports that LDCT screening of a high-risk population reduces lung cancer-related mortality. Both meta-analyses of EUnetHTA and Bonney et al. show similar conclusions, based on 8 RCTs. Sensitivity analysis including or excluding CXR screening in the comparator arm do not contradict each other. As Bonney et al. included mortality data of the UKLS trial and used latest planned time points for their analysis, we adopted it as the main result for lung cancer-related mortality in this report. The certainty of evidence for all-cause mortality was downgraded one level due to high risk of "other bias" in LUSI, NELSON, DANTE and MILD. A visualisation of the meta-analysis of Bonney et al. is provided in Figure 13.



Figure 13 – Meta-analysis of lung cancer-related mortality in LDCT screening, using latest planned time points



Source: Bonney et al. (2022)⁵¹

Paci = ITALUNG; Field = UKLS; Pastorino = MILD; Aberle = NLST; Infante = DANTE; De Koning = NELSON; Becker = LUSI; Wille = DLCST.



Key points

In people at high risk of lung cancer based on smoking history, screening with low dose CT scan reduces lung cancer-related mortality (RR 0.79, 95% CI 0.72 to 0.87; moderate-certainty evidence).

3.2.5. Lung cancer stage at diagnosis

A comprehensive overview of available evidence on lung cancer stages at different time points across studies is provided in Bonney et al. The evidence showed there was more stage I lung cancer detected in the LDCT group compared with control, across the time points. As time from randomization increased, there was probably no difference between groups for stage II and III lung cancer. In later time points, the evidence showed there was reduced stage IV lung cancer in the LDCT screening group compared to the control group:

- At year 1, three trials provided comparative data (NLST, DLCST, LSS) with a total of 30 434 participants. A 52% decrease in stage IV lung cancer cases was observed in the LDCT screening group (n = 26) versus the control group (n = 54), RR 0.48, 95% CI 0.30 to 0.77. NLST had a weight of 94% in this analysis.
- At year 2, two trials were included (NLST, DLCST) with a total of 28 774 participants. A non-significant decrease in stage IV lung cancer cases was observed in the LDCT screening group (n = 37) versus the control group (n = 46), RR 0.80, 95% CI 0.52 to 1.24. NLST had a weight of 95% in this analysis.
- At 5 to 10 years post-randomisation, four trials were included (LUSI, UKLS, DANTE and ITALUNG) with a total of 13 676 participants. 45% fewer cases of stage IV lung cancer were detected in the LDCT screening group (n = 65) than in the control group (n = 110), RR 0.55, 95% CI 0.34 to 0.91.

- At more than 10 years after randomisation, four trials were included (NLST, DLCST, MILD and ITALUNG) with a total of 32 763 participants. 23% fewer cases of stage IV lung cancer were detected in the LDCT screening group (n = 553) than in the control group (n = 705), (RR 0.77, 95% CI 0.69 to 0.86).

Jonas et al. reports that all included trials reported more stage I cancers in LDCT groups than in control groups with an absolute increase in stage I lung cancers of 19 percent. Included studies show increases in early stage (I-II) and decreases in late stage (III-IV) lung cancer incidence, representing stage shift.

The EUnetHTA authors did not report on lung cancer stages as they argue that a stage shift as such is not a patient-relevant outcome and benefits of screening must ultimately be reflected in the mortality outcome.

Discussion

An increase of stage I lung cancer diagnoses across time points is consistently observed across all individual trials. As an unknown extent of these stage I lung cancers represent overdiagnosed cases, care should be given to consider this increase of stage I lung cancer diagnoses as a benefit of lung cancer screening (this will be discussed more in detail in the paragraph on overdiagnosis). In later time points, however, all available data (from 7 individual trials) support an absolute decrease of stage IV lung cancer diagnosis.

Key points

In people at high risk of lung cancer based on smoking history, screening with low dose CT scan results in a reduction of stage IV lung cancer diagnoses (at 5 to 10 years post randomisation: RR 0.55, 95% CI 0.34 to 0.9, moderate-certainty evidence ; at ≥ 10 years post-randomisation: RR 0.77, 95%CI 0.69 to 0.86, moderate-certainty evidence).



3.2.6. Health-related quality of life (HRQoL)

Evidence retrieved from included trials

Psychosocial consequences were evaluated in only four trials (NLST, NELSON, UKLS, DLCST), with different questionnaires used for assessment (EQ-5D, STAI-6, HADS, COS-LC and others). Bonney et al. estimated the evidence for psychosocial consequences of low quality due to inconsistencies in outcome measures, sample groups, and timing of assessments. Overall, no long-term adverse consequences on HRQoL were reported.

The EUnetHTA authors state that the results for psychosocial consequences of screening were not very meaningful because of lack of statistical significance or questionable relevance. They report on the same four studies as Bonney et al.

Jonas et al. report that the trials only evaluated short-term quality of life, but none evaluated quality of life over the longer course of the trial. In a subset of the NELSON participants, indeterminate results lead to short-term increases in distress which had resolved at 2-year follow-up.⁶⁸

As the limited evidence available from included trials is not sufficient to inform the economic model inputs for the Belgian economic evaluation, a 6.1.7.9.

Key points

- The limited evidence available from LDCT trials does not suggest any long-term adverse impact on HRQoL with LDCT screening (low-certainty evidence).
- To inform the economic model inputs for the Belgian economic evaluation, an additional targeted (non-systematic) search for QoL will be performed in 6.1.7.9.

3.2.7. False positive results and consequences

All three systematic reviews provided tables with false positive rates and the number of invasive tests performed for false positive rates for each included RCT. A summarized overview of false positive rates, subsequent invasive tests (e.g., biopsies, surgical procedures) or therapeutic interventions (e.g., video-assisted thoracoscopy (VATS), thoracotomies) and complications of these interventions is provided in Table 8 and Table 9. When discrepancies were detected between systematic reviews, individual studies were assessed for clarification.

Generally, two different definitions of false positive results were identified within the systematic reviews and individual studies:

- Any result that is not a negative screen (including indeterminate scans), in participants who subsequently did not have lung cancer.
- Any result that requires further invasive diagnostic investigation (e.g., biopsy, surgical procedure), in participants who subsequently did not have lung cancer, with exclusion of indeterminate scans that were followed-up with repeat scans only.

We emphasize this use of different definitions, as this leads to vastly different results. For instance, the NELSON trial included an intermediate test result category which subsequently led to a relatively low false positive rate (1.2% over all rounds). Nevertheless, nearly 20% of the participants had indeterminate or suspicious lung nodules at baseline, of whom 95% eventually tested negative for lung cancer.⁶⁹ Across all four screening rounds in the NELSON trial, nearly 10% of LDCT screens led to an indeterminate test result.

In the UKLS trial, which is a single screen RCT, 46% of subjects underwent at least one further CT after the initial screen, whereas the trial authors defined false positives as those requiring further diagnostic investigation more immediately than a repeat annual screen, but who subsequently did not have lung cancer (4%).



We decided to report indeterminate or suspicious lung nodules, which eventually turn out not to be malign, to be false positive screening results. Thus, abnormal screening results which were examined both with imaging diagnostics (earlier than the next planned LDCT screen) and/or with invasive diagnostic procedures are considered in this report.

Table 8 – False positive rates reported by individual RCTs

Trial	N part.	Screening intervals (years)	Main definition of positive nodule	False positive rates /screening round	
NLST	26 723	0,1,2	≥4mm	R0: 26% R1: 27% R2: 16%	
NELSON	7900	0,1,3,5,5	>50mm ³	R0: 20%* R1: 7% R2: 9% (males only) R3: 4% (males only)	
LSS	1660	0,1	R0: >3mm R1: ≥4 mm	R0: 19% R1: 25%	
MILD	2376	0-6 (annual) 0,2,4,6,8 (biennial)	>60 mm ³	Annual R0:14% R1: 3% R2: 4% R3: 2% R4: 2% R5: 1% R6: 3%	Biennial R0:13% R1: 2% R2: 3% R3: 4%
DANTE	1264	0,1,2,3,4	≥10 mm	NR	
DLCST	2052	0,1,2,3,4	≥5mm	R0: 8% R1: 2% R2: 2% R3: 2%	



Trial	N part.	Screening intervals (years)	Main definition of positive nodule	False positive rates /screening round
				R4: 2%
ITALUNG	1613	0,1,2,3	≥5mm	NR
LUSI	2029	0,1,2,3,4	≥5mm	R0: 21% R1: 4% R2: 3% R3: 5% R4: 5%
UKLS	1987	0	>50 mm ³	R0: 46%**

* When defined as any work-up, including follow-up scans for indeterminate results. When excluding indeterminate results, false positive rates are 1%, 1%, 4% and 1% at subsequent screening rounds, respectively

** When defined as any work-up, including follow-up scans. When defined as referral to pulmonologist, false positive rate is 4%

Abbreviations: NR = not reported.

Table 9 – False positive evaluations and complications

Trial	N part.	Invasive procedures n (%)	Complications (%)
NLST	26 723	Needle biopsies: 66 (0.25)	Intermediate: 6 (0.02) Minor: 1 (0.004)
		Bronchoscopy: 227 (0.85)	Major: 2 (0.007) Intermediate: 9 (0.0034) Death within 60 days: 4 (0.015)
		Thoracotomy, thoracoscopy, or mediastinoscopy: 164 (0.61)	Major: 9 (0.034) Intermediate: 13 (0.049) Minor: 4 (0.015) Death within 60 days: 2 (0.007)
NELSON (After 3 rounds of screening)	7900	Bronchoscopy: 135 (1.71)*	Major: 0
		Thoracotomy or VATS: 47 (0.59)	Major: 3 (0.04) Minor: 20 (0.25)**
LSS	1660	NR	NR
MILD	2376	Needle biopsies: 4 (0.17)	NR



Trial	N part.	Invasive procedures n (%)	Complications (%)
		Lung resections: 3 (0.13)	NR
DANTE	1264	Thoracotomy, VATS, or mediastinoscopy: 17 (1.33)	NR
DLCST	2052	VATS: 7 (0.34)	Minor: 2 (0.10)
ITALUNG	1613	Bronchoscopy: 16 (1.00)	NR
		Lung resections: 4 (0.25)	NR
LUSI	2029	Needle biopsies: 9 (0.44) (Only first round of screening)	NR
UKLS	1987	Needle biopsies: 7 (0.35)	NR
		EBUS: 1 (0.05)	NR

* Data retrieved from van 't Westeinde et al. (2012)⁷⁰ Of note, the number of bronchoscopies for false positives in the NELSON trial is between 130 and 140, therefore we assumed a number of 135. ** Data retrieved from van 't Westeinde et al. (2012)⁷¹

Some differences are observed between these data and those reported in EUnetHTA

Abbreviations: NR = not reported

Overall, false positive rates at baseline varied between 8% and 46% at baseline screening and decreased with subsequent LDCT screens. Bonney et al. reported an overall false positive rate from baseline LDCT of 21% (8874/41 857 screens), thereby counting a false positive rate from baseline of 1% in the NELSON trial (as reported by the trial authors). All three review authors acknowledge that the wide range of false positive rates between RCTs was attributed to the differences in eligibility criteria and radiological definition of nodule size and volume used as the threshold between a positive and negative screen. Surgery on individuals with benign findings was performed in 0.1%–1.3% of the participants invited for screening.

Discussion

Given the wide range of false positive screens and consequent invasive procedures, no point estimates are provided for these outcomes but rather a range (minimum, maximum) of observed rates in individual trials. No uniform definition of false positive screening results was used. Data from LDCT trials are limited regarding harms of screening as a consequence of

false positive results, as shown in Table 9. Regarding subsequent invasive tests and surgical procedures, there was no uniform categorisation of interventions. Moreover, complications of these interventions were reported only in three trials, with one trial reporting surgical outcomes before the final screening round. Overall, we rate the available evidence from RCTs regarding false positive rates and consequences as low-quality.

Three trials reported on bronchoscopies for false positive results, which varied between 0.85 and 1.71% of participants. However, the role of bronchoscopy in a lung cancer screening protocol has been questioned in a supplementary publication of the NELSON trial.⁷⁰

**Key points**

- We consider abnormal screening results which were examined both with imaging diagnostics (earlier than the next planned LDCT screen) and/or with invasive diagnostic procedures as false positive results in this section.
- Lung cancer screening with LDCT is associated with a false positive rate between 8% and 46% in the first screening round which decreased with subsequent screening rounds (low-certainty evidence).
- Lung cancer screening with LDCT results in invasive procedures for false positive findings in 0.1%–1.7% of the participants invited for screening, with few trials reporting complications of these procedures (low-certainty evidence).

3.2.8. False negative results and consequences

Bonney et al. reported small numbers of false negatives of five trials (NLST, NELSON, UKLS, MILD, DANTE).

Jonas et al. provided a table with the accuracy of LDCT for lung cancer screening in RCTs (see Table 10). The mean negative predictive value of included trials was 99.2% (range 97.7%-99.9%).

EUnetHTA did not report any false negative rates of included trials, as data on consequences of false negative screening results were not reported in the studies. The study authors state that the influence of the lack of specific data on consequences of false negative screening results on the harm-benefit balance is estimated to be small.

Table 10 – Accuracy of LDCT screening in included RCTs (Jonas et al.)

Trial Year of publication Location	N part. N contr.	Screening intervals (years)	Threshold for positive nodule result	Sensitivity Specificity	Positive predictive value Negative predictive value
NLST ⁵² 2011 USA	26 723 26 723	0,1,2	≥4 mm maximum diameter	Sn 93.1 Sp 76.5	PPV 3.3 NPV 99.9
NELSON ¹⁰ 2020 Belgium-Netherlands	7900 7892	0,1,3,5.5	Volumetric	Sn 59.0 Sp 95.8	PPV 43.5 NPV 97.7
LSS ⁵³ 2005 USA	1660 1658	0,1	≥3 mm maximum diameter	Sn NR Sp NR	PPV 7.0 NPV NR
MILD ⁵⁵ 2012 Italy	2376 1723	0-6 (annual) 0,2,4,6,8 (biennial)	Volumetric	Sn 68.5 (annual) Sn 73.5 (biennial) Sp 99.2	PPV 40.6 (annual) PPV 42.4 (biennial) NPV 99.8



Trial Year of publication Location	N part. N contr.	Screening intervals (years)	Threshold for positive nodule result	Sensitivity Specificity	Positive predictive value Negative predictive value
DANTE⁵⁶ 2015 Italy	1264 1186	0,1,2,3,4	>5 mm average diameter	Sn 79.5 Sp 75.5	PPV 18.6 NPV 98.1
DLCST⁵⁷ 2016 Denmark	2052 2052	0,1,2,3,4	Volumetric	Sn NR Sp NR	PPV 9.5 NPV NR
ITALUNG⁵⁸ 2017 Italy	1613 1593	0,1,2,3	≥5 mm average diameter	Sn 95.0 Sp 26.4	PPV 3.6 NPV 99.4
LUSI⁵⁹ 2020 Germany	2029 2023	0,1,2,3,4	≥5 mm average diameter	Sn 93.5 Sp 62.0	PPV 7.2 NPV 99.7
UKLS⁶⁰ 2021 UK	2028 2027	0	Volumetric	Sn 75 Sp NR	PPV 36.6 NPV NR

Abbreviations: Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; NR = not reported.

**Key points**

- Small numbers of false negatives were reported in a number of trials, and data on consequences of false negatives were not reported in LDCT trials.

3.2.9. Overdiagnosis

Overdiagnosis rates were estimated for eight individual trials across the three systematic reviews and were measured using the difference in cancer incidence rates in the screened group compared with the control group (excess-incidence approach). Two different measures of overdiagnosis were used, depending on the denominator used:

- Pa (proportion of all lung cancer cases): the ratio between excess incidence (calculated as the difference between the cumulative incidence of lung cancer in the screening and control arms) and the cumulative incidence of all lung cancers (screen-detected and non screen-detected) in the screening arm
- Ps (proportion of screen-detected cases): the ratio between excess incidence and the cumulative incidence of screen-detected lung cancers.⁷²

The latter measure is considered more suitable when informing an individual eligible screening participant about pros and cons of screening, as it represents the risk that a screen-detected cancer is overdiagnosed (i.e., what is the likelihood that the cancer is overdiagnosed should you be detected with a cancer in the screening programme).⁷³ In other words, if we refer to someone as being overdiagnosed by screening, the cancer must be screen-detected.⁶⁴

The duration of planned follow-up differed between trials, ranging between 3.8 and 9.3 years of follow-up from the last screen. Several trials also provided extended follow-up data after planned follow-up points, showing reduced numbers of excess cases in the screened group, and thus reduced overdiagnosis rates.

Not all individual trials provided data regarding contamination rates of the control groups during follow-up. Contamination is defined as the proportion of the control group who have been screened; the higher the contamination rate, the more the estimate of overdiagnosis is biased towards the null.⁷³

Table 11 provides an overview of overdiagnosis estimates (Ps and Pa) in lung cancer screening trials. Overdiagnosis estimates which were not available in individual trial publications, were retrieved in a recent publication of Li et al.⁶⁴ They conducted a systematic review to identify estimates of overdiagnosis from RCTs of LDCT screening and calculated missing overdiagnosis estimates based on published numbers of cases or incidence.


Table 11 – Overdiagnosis rates from lung cancer screening RCTs

Trial	N part.	Screening intervals (years)	Follow-up time after last screen (years)	Overdiagnosis <Screen-detected cases Ps	Overdiagnosis <All lung cancers Pa	Contamination rate	Comment
NLST	26 723	0,1,2	4.5	18.5%	11%	Average annual rate of CT in CXR group: 4.3% (Jonas et al.)	CXR control
			Extended 9.3	3.1%	1.2%		
NELSON	7900	0,1,3,5.5	4.5	19.7%	12.0%	In the first 24 months after randomization 3.1% of the respondents received a lung cancer screening examination ⁷⁴	Only relevant for male participants
			Extended 5.5	8.9%	NR*		
MILD	2376	0-6 (annual) 0,2,4,6,8 (biennial)	3.8	21.5%	15.6%	By 10-year follow-up, 1.2% of control group had LDCT (Jonas et al.)	
DANTE	1264	0,1,2,3,4	4.4	41.3%	26.2%	3 years post-randomisation 68/1186 received CT scan: 5.7% (Bonney et al.)	Included CXR and sputum cytology for both trial groups pre-screening, and had a median follow-up of < 10 years
DLCST	2052	0,1,2,3,4	5	67.2%	44.8%	7.4% at end of screening, 20.3% at 5-year follow-up ⁷³	
ITALUNG	1613	0,1,2,3	5.5 8.3	-27%	-11.3%	NR	



Trial	N part.	Screening intervals (years)	Follow-up time after last screen (years)	Overdiagnosis <Screen-detected cases Ps	Overdiagnosis <All lung cancers Pa	Contamination rate	Comment
LUSI	2029	0,1,2,3,4	5.7	25.4%	17.8%	13% at 10 years post randomisation: 264 participants in the control arm had received a CT. (Bonney)	
UKLS	1987	0	7.2	25.6%	12.5%	NR	

* The proportion of screen-detected cancers in the screened group were not available

Source: Li et al. (2022)⁶⁴

Abbreviations: NR = not reported

EUnetHTA and Jonas et al. did not provide a summary overall estimate of overdiagnosis but rather a range of point estimates of the individual studies. The EUnetHTA authors state that proportions between the studies varied so much that an overall estimate could not be interpreted meaningfully. They did not identify concrete reasons for the heterogeneity of the results, such as individual aspects of the screening strategy and characteristics of the study population. They conclude that risk of overdiagnosis related to those with a lung cancer diagnosis during the screening phase (Ps) varied greatly between studies, ranging from 0% (no overdiagnosis in the ITALUNG study) to 63% (in the DLCST study).

Jonas et al. reported a similar overdiagnosis estimate range (Ps) from 0% to 67% across individual trials. They judged the strength of evidence for this outcome as low, given inconsistent and imprecise findings. Furthermore, the inadequate duration of follow-up and heterogeneity limit the evaluation.

Bonney et al. performed a meta-analysis only with studies comparing LDCT screening to no screening thus excluding the NLST trial, and with a median follow-up of more than 10 years after randomization. Their estimated overdiagnosis in relation to all individuals invited for screening (Pa) was 18%, however the 95% CI was 0 to 36% (180 more lung cancers

overdiagnosed per 1000 lung cancers detected (0 more to 360 more); 5 trials, low-certainty evidence).

Discussion

While different definitions of overdiagnosis are being used, care should be taken not to confound different measures. The overdiagnosis estimate provided by Bonney et al. was 18% (CI 0-36%) of all lung cancer cases (Pa), whereas the Ps estimate of the same 5 trials is 38% (CI 14-63%).⁷³ We prefer presenting overdiagnosis as proportion of screen-detected cases (Ps) as it is the most patient-relevant outcome.

EUnetHTA rated the quality of the evidence for overdiagnosis as high, as the majority of studies are high-quality and support the view that LDCT screening leads to overdiagnosis (with range estimates provided). However, we would agree with Jonas and Bonney et al. to judge the strength of evidence as low-quality given inconsistent and imprecise findings. As overdiagnosis estimates largely depend on duration of follow-up, they should therefore be interpreted in the context of postscreening follow-up. In a recent publication, Li et al. suggest that differences in postscreening follow-up time partially explain variation in overdiagnosis estimates across



lung cancer screening trials. Using a modelling study, they report that 39% of the variation in overdiagnosis estimates was explained by postscreening follow-up time.⁶⁴

Extended follow-up data are valuable when assessing overdiagnosis as they reduce lead-time bias, but in turn could lead to inaccuracies of ascertaining lung cancer incidence and thus overdiagnosis. However, it should be noted that ascertaining lung cancer incidence is less prone to detection bias than ascertaining disease-specific mortality for instance.

Contamination rates, defined as the proportion of the control group who have been screened, are not well described across trials as shown in Table 11. While an important drop in the overdiagnosis estimate has been observed at the (unplanned) extended follow-up of the NELSON trial, it should be noted that the contamination rate was only determined for a sample of male subjects of the control arm. In the first 2 years after randomization 3.1% of the respondents received a lung cancer screening examination, which was assessed by sending a questionnaire (with a response rate of 73%).⁷⁴ The contamination rate at 11 years after randomization remains unknown but it could have biased the overdiagnosis estimate to the null. In the DLCST trial, the contamination rate was assessed using data from registries and was 7.4% until the end of screening (4 years post randomisation) and 20.3% at 5-year follow-up (10 year post randomisation).^{73, 75}

Key points

- Overdiagnosis estimates range from 0% to 67% of screening detected cancers (Ps) across individual LDCT trials (low-certainty evidence).
- As overdiagnosis estimates largely depend on duration of follow-up, they should therefore be interpreted in the context of postscreening follow-up.
- Contamination rates, defined as the proportion of the control group who have been screened, are not well described across trials although they bias the estimate of overdiagnosis towards the null.

3.2.10. Incidental findings

Although the aim of lung cancer screening is to detect pulmonary nodules that could indicate early-stage lung cancer, LDCT scans of the chest may also detect other pulmonary and extrapulmonary abnormalities.⁷⁶ These incidental findings (IFs) (also called incidentalomas) are thus discovered unintentionally, and may cause benefit or harm the participant, while their management adds costs and workload to the health care system. Within the retrieved evidence, there are varying definitions of what constitutes a 'clinically relevant', or 'reportable', or 'actionable' finding and a lack of standardised reporting of IFs.

Evidence retrieved from included trials

Bonney et al. provided an overview of incidental findings (IFs) reported in six trials (NLST, NELSON, DEPISCAN, DANTE, UKLS, DLCST). They state that IFs are likely common but not well described across the included trials, with varying categories of findings reported. EUnetHTA did not perform a systematic investigation of IFs on LDCT screening, as information on such events and their consequences is only available for the screening groups. The review authors argue that it remains unclear whether these findings benefit or harm individuals. Jonas et al. reported screening related IFs derived from three RCTs (NLST, NELSON, UKLS). However, there was no



standard definition of what constitutes an IF, nor which findings were clinically significant or actionable.

We provided an overview of the IFs from the included trials in Table 12. It can be concluded that LDCT screening leads to IFs, but these are not well characterized and their prevalence varies across individual trials. Furthermore, it remains unclear whether these findings benefit or harm individuals. Not only the prevalence, but also the downstream management

and outcomes of significant IFs should be assessed to quantify health gains or losses in light of a lung cancer screening program. As LDCT screening leads to IFs in multiple anatomical regions and the clinical significance of a number of these findings is unclear, determining the overall potential benefit or harm of IFs in LDCT screening is challenging. Moreover, the potential benefits or harms will partly depend on the population screened, screening methodology, and the healthcare system in which the screening program exists.⁷⁷

Table 12 – Incidental findings from lung cancer screening RCTs

Study	Participants (trial sample)	Screening rounds	Results on IFs	Categories of IFs
NLST				
Nguyen et al. ⁷⁸	17 309	3	59% of participants had one or more extrapulmonary findings, including 20% with findings categorized by radiologists as “potentially significant”.	Cardiovascular (atherosclerotic calcifications, aortic aneurysms): 8.5% Renal: 2.4% Hepatobiliary: 2.1% Adrenal: 1.2% Thyroid: 0.6% Extra-thoracic cancers: 0.39%
Gareen et al. ⁷⁹	26 455	3	A significant IF was reported for 8954 (34%) participants. 18% of LDCT screening examinations had at least 1 significant IF reported.	Calculated from Supplementary Table 3 ⁷⁹ , using 26 455 participants as denominator. A selection of reportable IFs is provided here: Coronary artery calcifications: 6.7% Renal mass: 2% Hepatic mass: 1.8% Adrenal mass: 0.8% Aortic aneurysm: 0.6% Bronchiectasis: 0.6% Mediastinal: 0.6% Thyroid nodule: 0.3% Emphysema: 21% Breast mass: 0.5%
Pinsky et al. ⁸⁰	26 722	3	Only incidental respiratory disease-related findings reported.	% of baseline screen: Emphysema: 31% Reticular opacities: 20% Pleural thickening: 6%



Study	Participants (trial sample)	Screening rounds	Results on IFs	Categories of IFs
				Noncalcified hilar/mediastinal adenopathy: 1.7% Atelectasis: 1%
Jassal et al. ⁸¹	26 722	3	Participants screened with LDCT had a modestly higher incidence of head and neck cancers (HNC), compared to CXR screening.	HNC was diagnosed in 191 participants in the LDCT (0.7%)
Loomans-Kropp et al. ⁸²	26 722	3	Only incidental findings related to thyroid cancer reported.	% of participants: 0.5% (n = 135), 0.2% (n = 83), and 0.2% (n = 73) had a thyroid-related abnormality at years 0, 1, and 2, respectively
NELSON				
van de Wiel et al. ⁸³	1929	1	In 73% of the participants, clinically not relevant IFs (as defined by the authors) were identified. 129 participants (7%) had a total of 144 clinically relevant IFs. Additional imaging was performed mainly by ultrasound. Of note, 99% of the participants in this sample were male.	Clinically relevant IFs: Hepatic lesions: 3.9% Renal lesions: 2.7% Thyroid: 0.5% Other: 0.3% Not clinically relevant IFs: Pulmonary fibrosis: 6% Bronchiectasis: 0.2% Emphysema: 17% Pleural calcifications: 2.6% Pleural plaques: 3.4% Small lymph nodes: 0.3% Coronary artery calcifications: 68% Adrenal lesions <10HU: 0.7%
MILD				
Sabia et al. ⁸⁴	2239	1		Coronary artery calcium score (CAC): 0 (absent): 5.6% 1-10 (minimal): 31.2% 11-100 (mild): 32.6% 101-400 (moderate): 17.6% >400 (severe): 13.1%
DLCST				



Study	Participants (trial sample)	Screening rounds	Results on IFs	Categories of IFs
Saghir et al. ⁸⁵	2052	5	140 participants (7%) had 148 clinically significant incidental findings	Larynx: 1 (0.05%) Thyroid: 3 (0.1%) Gastro-esophageal: 9 (0.4%) Breast: 16 (0.8%) Cardiac: 5 (0.2%) Mediastinum: 12 (0.6%) Aorta: 28 (1.4%) Liver and gallbladder: 18 (0.9%) Pancreas: 6 (0.3%) Spleen: 1 (0.05%) Intestines: 2 (0.1%) Kidneys: 40 (1.9%) Skin: 2 (0.1%) Chest-wall: 3 (0.1%) Vertebral column: 2 (0.1%)
ITALUNG				
Mascalchi et al. ⁸⁶	1364	1	Coronary artery calcification (CAC) were absent in 470 (34.5%), mild in 433 (31.7%), moderate in 357 (26.2%) and severe in 104 (7.6%) subjects.	
Mascalchi et al. ⁸⁷	536	1	Mild emphysema was present in 14.9% and moderate-severe in 17.4% of participants. CAC were present in 67% of subjects (mild in 34.7%, moderate-severe in 32.2%).	
UKLS				
Field et al. ⁸⁸	1994	1	Significant incidental findings not related to thoracic malignancy but regarded by both the central and local reader as likely to be clinically significant, were referred back to the participant's general	4 aortic dilatations (0.2%), 5 severe aortic valve calcifications (0.3%), 4 mediastinal masses (0.2%), 6 mediastinal or hilar lymphadenopathy (0.3%), 41 pneumonias (2.1%), 5 bronchiectasis (0.3%), 8 pleural thickening (0.4%), 7 smoking related interstitial lung diseases (0.4%), 9 severe emphysemas (0.5%), 6 unspecified interstitial fibrosing lung disease (0.3%), 2 nonspecific interstitial pneumonias (0.1%), 12 usual



Study	Participants (trial sample)	Screening rounds	Results on IFs	Categories of IFs
			practitioner in 128 participants (6.4%). In such cases, a formal report with recommendations for further management was sent from the local site to the GP.	interstitial pneumonias (0.6%), 1 sarcoidosis (0.1%), 2 oesophageal thickening or dilatation (0.1%), 1 breast mass (0.1%), 2 lobar collapse (0.1%), 1 biliary dilatation (0.1%), 3 adrenal masses (0.2%), 1 liver cirrhosis (0.1%), 1 hydronephrosis (0.1%), 1 liver mass (0.1%), 1 pancreatic cyst (0.1%), 3 renal masses (0.2%), 1 splenomegaly (0.1%), and 1 thyroid mass (0.1%)
DEPISCAN				
Blanchon et al. ⁵⁴	385	1		19 severe emphysema (4.9%), 63 bronchiectasis (16%), and 18 mediastinal findings (4.7%)
DANTE				
Infante et al. ⁵⁶	1264	1	Only malignancies reported	1 lymphoma, 1 oesophageal carcinoma, 1 malignant mesothelioma, 1 colon cancer with liver metastasis, and 2 renal cancers with pulmonary metastasis

As the evidence from included trials regarding prevalence of IFs is scarce, we sought to assess the prevalence of incidental findings using data of non-randomized studies including pilot studies. Even though the results of this additional literature search will not allow to draw a conclusion on the harms/benefit balance of IFs, information about their prevalence should be incorporated into the shared decision-making process with potential participants and can serve as an indication of the additional clinical workload they may generate.

Exploratory analysis of prevalence of IFs that require additional examination

Jonas et al. included observational studies in their systematic review and identified 4 additional uncontrolled studies that described rates of “significant” incidental findings in LDCT-screened populations. These studies reported a wide range of screening-related incidental findings (4% to 40%) that were estimated significant or requiring further evaluation.⁵⁰ Since the search range of Jonas et al. was from inception to May 2019 with surveillance of literature until March 2020, we performed an additional

systematic search of studies describing IFs associated with LCS with a search range from January 2019 to June 23rd, 2023. A targeted approach was used as a comprehensive search for IFs in LCS would require an exhaustive search strategy for all relevant IFs recorded in different anatomical regions and would therefore be too time-consuming for this project. Only PubMed was searched, using the same search string for “LDCT” and “screening” as we used for searching SRs about effectiveness and harms of LDCT screening. For “incidental findings”, a combination of MESH-terms and free text words was used as shown in the Appendix. Both observational and randomized studies were considered, using a pre-specified inclusion criterium of at least 1000 LDCT screened participants at high risk of LC (as defined by the authors). The search for studies describing IFs in PubMed yielded 211 records, and finally 20 studies were included (see Figure 42). Pinsky et al. and Loomans-Kropp et al. are included in Table 12 as they report on samples of the included trials, and these studies were not yet identified through updating Bonney et al. An overview of IFs reported in the included observational studies is provided in Table 105.



During one of the expert meetings of this project, the ERS/ESTS/ESTRO/ESR/ESTI/EFOMP Statement on Management of Incidental Findings from Low-Dose CT screening for Lung Cancer was shared with the project team.²⁹ This European collaborative group propose a standardised approach of reporting and managing incidental findings. They identified twenty-three IF categories and provided suggestions for reporting and follow-up actions when these IF are identified. To estimate the prevalence and impact of IFs identified during LDCT screening, we listed the suggested actions from the ERS Reference Guide together with the prevalences of IFs we identified both in LCS trials and observational studies in Table 13. For each incidental finding category (23 in total, as shown in Table 2 of O'Dowd et al.²⁹), we estimated a range of participants who would require follow-up and provided which clinical or radiological examination is proposed in such case, as well as the health practitioners that would probably be involved. The reasons for excluding a reported prevalence from the final range estimate are clearly articulated (e.g., no information provided on severity; or isolated outlier). As an example, the reported prevalence of hepatic, renal or breast lesions in the UKLS trial were around a 10-fold lower than those reported in all other included studies. On the other hand, we excluded the (moderate to severe) CAC prevalence from the Italian trials (MILD and ITALUNG), which were about 6-fold higher than results from all other included studies. By combining the range estimates of the different incidental findings categories, we calculated the proportion of LCS participants that would require an additional examination for at least one incidental finding. We assumed no correlation between the different categories of incidental findings.

Using the suggested actions from the ERS Statement and the reported prevalences of IFs from our literature search, we estimated that **twenty-three percent of LCS participants would have at least one incidental finding** for which an additional examination is suggested. This proportion depends largely on the prevalence of moderate to severe coronary artery calcification and moderate to severe emphysema. These two incidental findings provide an opportunity to assess for cardiovascular disease and COPD, respectively, but also allow a re-evaluation of the lung cancer risk of participants, as well as the risk of competing causes of death.²⁰ Although this could alter the balance of benefits and harms of screening for

participants, further research is warranted to assess the potential health gains or losses from these incidental findings. When excluding these two incidental findings from our exploratory analysis, and considering them as reportable for research purposes only (a strategy that is applied in several pilot studies (e.g., the SUMMIT study)), we estimate that about thirteen percent of LCS participants would require an additional examination for an incidental finding.

This analysis is characterized by several limitations. First of all, no quality assessment of included observational studies was performed. Often, there was no consistent reporting or standardized definitions of incidental findings across studies, which poses a challenge in associating them with the recommended actions outlined in the ERS Statement. The population included and the methods for defining a high-risk population varied among the studies. We also acknowledge that LDCT trials employed imaging protocols different from those currently employed in lung cancer screening pilot studies, so that the prevalence of incidental findings may differ. Consequently, one could advocate for prioritizing incidental findings prevalences from pilot studies as they more accurately reflect current practice, but we preferred to include the results from the trials to provide a comprehensive overview. Finally, the majority of included studies only reported IFs from the baseline scan. Although a majority of incidental findings would especially generate additional examinations after the baseline scan, some categories of IFs (e.g., consolidation as a manifestation of pulmonary infection) would also occur in subsequent screening rounds. Results from the Manchester Lung Health Check pilot are relevant to this subject: among 1409 participants who were offered two rounds of annual LDCT screening, eleven percent had potentially clinically significant incidental findings (CAC and emphysema were not included), of which 8% at baseline.

Despite these limitations, we observed consistent prevalences across studies for many of the incidental finding's categories. The results of this exploratory analysis indicate that, when applying the ERS/ESTS/ESTRO/ESR/ESTI/EFOMP Statement on Management of Incidental Findings, an additional examination can be expected in about 23% of participants. If coronary artery calcification and emphysema would



be excluded and reportable for research purposes only, this would be reduced to an additional examination in about 13% of participants (1 in 8 participants). As mentioned earlier, it is important not only to evaluate the prevalence but also to assess the downstream management and outcomes of significant incidental findings in order to quantify the health gains or losses of incidental findings associated with a lung cancer screening program.

Several UK LCS pilots provide information on the downstream management of IFs. In the beforementioned Manchester Lung Health Check pilot, the threshold of significance of IFs was at the radiologists' discretion and coronary artery calcification and emphysema were not reported. Clinical management of IFs required specialist reviews in 6%, medication changes in 2.4% and interventional treatments in 0.71 % of participants respectively, and resulted in the diagnosis of an extra-pulmonary malignancy in 0.36% of

participants. Of note, the screening team took responsibility for specialist referrals to reduce the burden on primary care. In the West London pilot, 10% of participants were referred to primary care for IFs and patient management changes occurred in 23% of referred participants. In the SUMMIT study, a standardised reporting and management protocol for incidental findings during baseline LDCT led to review for only 1 in 20 and 1 in 25 participants in primary and secondary care, respectively. Of note, CAC and emphysema were reportable for research purposes only and the publication does not include IFs suspicious for extrapulmonary malignancy, which will be reported in a planned publication. Finally, the proportion of participants who actually attended a primary care appointment following referral was relatively low (between 33% and 57%).

Table 13 – Overview of incidental findings categories, reported prevalence and estimated impact

Incidental findings category (n = 23) ²⁹	Suggested action (ERS Statement on IFs) ²⁹	Reported prevalence, percentage of participants	Impact
			- Range estimate of participants who require an additional examination - Proposed follow-up examination - Involved health care practitioners
Emphysema	Report moderate to severe for clinical assessment, using a qualitative classification: mild (<25%) moderate (25-50%) and severe >50%.	- NLST (Gareen et al.): 21% (all emphysema was considered reportable to the referring clinician) - NELSON: 17% (in total, considered not clinically relevant) - ITALUNG: 17.4% (moderate or severe, not assessed by visual assessment but with densitometry) - DEPISCAN: 4.9% (only severe) - UKLS: 0.5% (only severe, referred) - SUMMIT (Tisi et al.): 33% in total, 11.6% moderate to severe (qualitative grading by visual assessment, research purposes only)	- Moderate to severe: 3.9%-11.6% - Clinical review +/- spirometry - Primary care practitioner/pulmonologist



Incidental findings category (n = 23) ²⁹	Suggested action (ERS Statement on IFs) ²⁹	Reported prevalence, percentage of participants	Impact
			- Range estimate of participants who require an additional examination - Proposed follow-up examination - Involved health care practitioners
		- Henderson et al: 9.7% (3.9% follow-up recommended)	
Interstitial lung abnormality (ILA)	Surveillance as part of a screening programme or ILA involving more than 5% of either the whole lungs or a lung zone could be referred for specialist review	- SUMMIT (Tisi et al.): 4.8% in total (moderate 0.6%, severe 1%) - Manchester pilot (Balata et al.): 3.9%	- Unclear - Screening program/specialist review - Screening program/pulmonologist
Bronchiectasis	Refer for clinical assessment if moderate or severe	- NELSON: 0.2% (considered not clinically relevant, no details provided) - NLST (Gareen et al.): 0.6% (considered reportable to the referring clinician) - UKLS: 0.3% (referred) - DEISCAN: 16% (in total, no details on severity) - Henderson et al: 4.5% (1.7% follow-up recommended) - SUMMIT (Tisi et al.): 7.4% in total, moderate to severe 0.94% - Manchester pilot (Bradley et al.): 0.4% (potentially significant)	- Moderate to severe: 0.3-1.7% - Clinical assessment - Primary care practitioner/pulmonologist
Respiratory bronchiolitis interstitial lung disease	Smoking cessation referral		- No additional impact, as smoking cessation would be included in LCS program
Consolidation	Refer to lung cancer service if cancer is possible Repeat CT at 6 weeks or 3 months if likely inflammatory	- NLST (Gareen et al.): 0.6% (considered reportable to the referring clinician) - Manchester pilot (Bradley et al.): 2.3% (proposed antibiotics)	- 0.6-2.3% - Repeat CT, clinical assessment - Pulmonologist



Incidental findings category (n = 23) ²⁹	Suggested action (ERS Statement on IFs) ²⁹	Reported prevalence, percentage of participants	Impact - Range estimate of participants who require an additional examination - Proposed follow-up examination - Involved health care practitioners
Pleural effusion/thickening	Refer for clinical assessment and work-up if suspicious appearances including a new effusion, malignant appearing pleural thickening or mass	- UKLS: 0.4% (all thickening) - NLST (Pinsky et al.): 6% (all thickening)	- Unclear - Clinical assessment - Pulmonologist
Pleural plaques	Report when compensation is offered (asbestos)	- NELSON: 3.4% (considered not clinically relevant)	- No clinical activity should be generated
Tuberculosis	Referral into local TB service		- Unclear - Clinical assessment - Tuberculosis service/pulmonologist
Bronchial wall thickening	No action required		- Unclear
Coronary artery calcification (CAC)	Cardiovascular risk assessment if moderate or severe, simple visual scoring is able to stratify risk of adverse outcome Primary preventive measures	- NLST (Gareen et al.): 6.7% (considered reportable to the referring clinician) - NELSON: 68% (considered not clinically relevant) - MILD: 30.7% (moderate or severe) - ITALUNG: 33.8% (moderate or severe, using a 0–3 visual scale) - SUMMIT (Tisi et al.): 64% (total), 1.6% (moderate to severe, research purposes only) - Mendoza et al: 24% (considered significant, not classified as moderate or severe) - London pilot (Bartlett et al.): 5.5% (moderate or severe)	- Moderate or severe: 1.6-5.5% <i>We preferred the results of recent pilots for this prevalence range, excluding the high prevalence in ITALUNG and MILD.</i> - Cardiovascular risk assessment - Primary care practitioner



Incidental findings category (n = 23) ²⁹	Suggested action (ERS Statement on IFs) ²⁹	Reported prevalence, percentage of participants	Impact
			- Range estimate of participants who require an additional examination - Proposed follow-up examination - Involved health care practitioners
Aortic valve disease	Refer those with moderate or severe aortic valve calcification for evaluation with echocardiography	- Henderson et al: 13.3% (5.2% follow-up recommended)	
		- NLST (Gareen et al.): 0.2% (considered reportable to the referring clinician: moderate or greater) - UKLS: 0.3% (severe aortic valve calcifications, referred) - Kapoor et al: 0.3% (actionable IF) - London pilot (Bartlett et al.): 1.6% (moderate or severe) - Manchester pilot (Bradley et al.): 0.3% (potentially significant) - Tisi et al: 16% (total, research purposes only)	- Moderate or severe: 0.2-1.6% - Echocardiography - Cardiologist
Thoracic aortic calcification/ dilatation	Referral when aorta >40mm diameter cfr local guidelines	- NLST (Gareen et al.): 0.6% (>42mm) - UKLS: 0.2% (aortic dilatations, referred) - Kapoor et al: 1.2% (4/17 (24%) underwent endovascular surgery for dilated aorta) - London pilot (Bartlett et al.): 0.3% (referred) - Manchester pilot (Bradley et al.): 1.3% (36-51mm range, 11/19 (58%) required radiological surveillance without intervention within 5 years) - Henderson et al: 1.7% (0.9% follow-up recommended) - SUMMIT (Tisi et al.): 2.8% (>40mm)	- 0.2-2.8% - Diagnostic workup - Cardiologist
Mediastinal mass	Cystic lesions do not require further assessment	- NLST (Gareen et al.): 0.6% (reportable, not clearly cystic)	- 0.2-0.6%



Incidental findings category (n = 23) ²⁹	Suggested action (ERS Statement on IFs) ²⁹	Reported prevalence, percentage of participants	Impact
			- Range estimate of participants who require an additional examination - Proposed follow-up examination - Involved health care practitioners
	Options for management include surveillance as part of the screening programme or Work-up with PET/CT/MRI, depending on clinical assessment	- UKLS: 0.2% (referred) - DEPIscan: 4.7% (mediastinal findings, not otherwise specified) - Manchester pilot (Bradley et al.): 0.2% (potentially significant)	- Work-up with PET/CT/MRI or surveillance as part of the screening programme, depending on clinical assessment - Primary care practitioner/radiologist
Mediastinal lymph nodes	≥15mm short axis and no explainable cause refer for clinical assessment Surveillance options include short interval CT scan at 3- 6 months	- NLST (Gareen et al.): 0.4% (mediastinal lymph node, considered reportable to the referring clinician) - NLST (Pinsky et al.): 1.7% (noncalcified hilar/mediastinal adenopathy, reportable) - UKLS: 0.3% (referred) - Kapoor et al.: 0.9% (actionable) - Manchester pilot (Bradley et al.): 0.1% (potentially significant)	- 0.1-1.7% - Clinical assessment, interval CT scan - Radiologist
Thyroid abnormalities	Referral for further investigation for nodules ≥20mm or those with suspicious features	- NLST (Gareen et al.): 0.3% (considered reportable to the referring clinician) - NLST (Nguyen et al.): 0.6% (potentially significant abnormalities) - NLST (Loomans-Kropp et al.): 0.5% (potentially significant) - NELSON: 0.5% - DLCST: 0.1% - UKLS: 0.1% - Kinsinger et al.: 2.4% (likely require follow-up or further evaluation) - Kapoor et al.: 1.1% (actionable) - Manchester pilot (Bradley et al.): 0.6% (potentially significant)	- 0.1-2.4% - Diagnostic evaluation of thyroid (ultrasound +/- biopsy) - Radiologist/endocrinologist/surgeon



Incidental findings category (n = 23) ²⁹	Suggested action (ERS Statement on IFs) ²⁹	Reported prevalence, percentage of participants	Impact
			- Range estimate of participants who require an additional examination - Proposed follow-up examination - Involved health care practitioners
		- Seo et al: 4.8% (presence of any thyroid nodule on LDCT, South Korean population) - Henderson et al: 1.5% (1.2% follow-up recommended)	
Cardiac decompensation/ pericardial effusion	Referral for echocardiography/ clinical assessment for those with moderate/ large pericardial effusions	- NLST (Gareen et al.): 0.4% (considered reportable to the referring clinician) - Manchester pilot (Bradley et al.): 0.2% (cardiomegaly) and 0.1% (pericardial effusion)	- 0.3-0.4% - Clinical assessment/echocardiography - Primary care practitioner/cardiologist
Oesophageal lesions	Referral for further assessment according to local guidelines/ pathways	- NLST (Gareen et al.): 0.2% (considered reportable to the referring clinician) - DLCST: 0.4% - UKLS: 0.1% - Manchester pilot (Bradley et al.): 0.5% (potentially significant)	- 0.1-0.5% - Clinical assessment - Primary care practitioner/surgeon
Abdominal aortic aneurysm (AAA)	Referral for further assessment/ surveillance according to local guidelines/ pathways	- NLST (Gareen et al.): 0.16% (considered reportable to the referring clinician) - SUMMIT (Tisi et al.): 0.02% (referred for primary care assessment)	- 0.02-0.16% - Clinical assessment/ surveillance according to local guidelines - Primary care practitioner/cardiovascular surgeon
Breast nodules	Refer any breast lesion that is not previously known, or lesions that are not clearly cystic, and/or not coarsely calcified, for triple assessment according to local guidelines/pathways	<i>Percentage of female participants:</i> - NLST (Gareen et al.): 1.1% of women (121/10 833, calculated using supplementary Table 3 and Table 1) - DLCST: 1.8% (16/905 women) - UKLS: 0.2% (1/499 women)	- 1.1-3.9% - <i>We decided to exclude the result of UKLS as an exceptional outlier, around a 10-fold lower than those reported in all other included studies.</i> - Mammography/breast ultrasound/biopsy



Incidental findings category (n = 23) ²⁹	Suggested action (ERS Statement on IFs) ²⁹	Reported prevalence, percentage of participants	Impact
			- Range estimate of participants who require an additional examination - Proposed follow-up examination - Involved health care practitioners
		- Manchester pilot (Bradley et al.): 3.9 % (28/723 of women screened) - Swensen et al.: 2.7% (20/735 women screened)	- Radiologist/surgeon
Liver lesions	Benign features: sharp margin and homogenous low attenuation (≤ 20 Hounsfield Unit (HU)), (focal) fatty sparing or deposition do not require further investigation Lesions < 1cm: No further investigation (unless the patient is high risk- cirrhosis or other hepatic risk factors) Lesions ≥ 1cm and no benign features: Referral for further investigation with contrast-enhanced CT/ ultrasound/ MRI	- NLST (Nguyen et al.): 2.1% (potentially significant abnormalities) - NLST (Gareen et al.): 1.9% (considered reportable to the referring clinician) - NELSON: 3.9% (ultrasound was proposed for all these lesions, so without clinical judgement before additional imaging) - DLCST: 0.9% (liver and gallbladder) - UKLS: 0.1% - Kapoor et al: 0.7% (only steatosis, actionable) - Manchester pilot (Bradley et al.): 1.5% (potentially significant) - Henderson et al: 2.1% (1.2% follow-up recommended)	- 0.9-2.1% <i>We decided to exclude the result of UKLS as an exceptional outlier, around a 10-fold lower than those reported in all other included studies.</i> - Contrast-enhanced CT/ ultrasound/ MRI - Radiologist/surgeon
Renal lesions	Homogenous hypodense or hyperdense cysts < 3 cm do not require further investigation, larger lesions should be evaluated in the next screening round Soft tissue or mixed density renal mass >1cm - refer for further assessment with contrast-enhanced CT or MRI	- NLST (Nguyen et al.): 2.4% (potentially significant abnormalities) - NLST (Gareen et al.): 2% (considered reportable to the referring clinician) - NELSON: 2.7% (ultrasound was proposed for all these lesions, so without clinical judgement before additional imaging) - DLCST: 1.9% - UKLS: 0.2%	- 1.3-2.4% <i>We decided to exclude the result of UKLS as an exceptional outlier, around a 10-fold lower than those reported in all other included studies.</i> - Ultrasound, contrast-enhanced CT or MRI - Radiologist/urologist



Incidental findings category (n = 23) ²⁹	Suggested action (ERS Statement on IFs) ²⁹	Reported prevalence, percentage of participants	Impact
			- Range estimate of participants who require an additional examination - Proposed follow-up examination - Involved health care practitioners
		- Manchester pilot (Bradley et al.): 1.3% (potentially significant, radiologist's discretion) - Henderson et al: 2.4% (1.5% follow-up recommended)	
Bone abnormalities	Referral for risk assessment (+/- DEXA) and bone protection for HU ≤ 130 or >50% loss of vertebral height	- NLST (Gareen et al.): 0.05% (only fractures and lytic lesions described) - DLCST: 0.1% (vertebral column, not otherwise specified) - Manchester pilot (Bradley et al.): 0.8% (potentially significant, radiologist's discretion) - SUMMIT (Tisi et al.): 7.2% osteoporotic wedge fracture, 1.2% referred (>50% loss of vertebral height)	- 0.8-1.2% - Risk assessment (+/- DEXA) - Unclear
Adrenal lesions	Lesions < 10mm or <10HU in density do not require further investigation Lesions 10-40mm or with attenuation > 10HU can be followed up at the next annual screening round or referred for further evaluation with contrast-enhanced CT or MRI Adrenal lesions stable on CT over 12 months may not require further investigation	- NLST (Nguyen et al.): 1.2% (potentially significant abnormalities) - NLST (Gareen et al.): 0.8% (considered reportable to the referring clinician) - NELSON: 0.7% (adrenal lesions <10HU) - UKLS: 0.2% - Janssen et al: 0.8% (potentially significant) - Kapoor et al: 0.4% (actionable IF) - Manchester pilot (Bradley et al.): 0.1% (potentially significant)	- 0.1-1.2% - Surveillance as part of the screening programme/ contrast-enhanced CT or MRI - Radiologist/endocrinologist



Key points

- Incidental findings are common in LDCT screening, although it remains unclear whether they benefit or harm participants.
- Using the IFs categories and suggested actions from the ERS Statement on Management of Incidental Findings, we estimated that an additional examination for IFs can be expected in about 23% of screening participants. If coronary artery calcification and emphysema would be excluded and reportable for research purposes only, this would be reduced to 13% of screening participants.
- Potential harms associated with overdiagnosis and overtreatment of IFs should be minimized. It is recommended to employ standardized protocols for reporting and managing IFs.

3.2.11. Radiation exposure

Radiation exposure in included trials

Only few included trials estimated cumulative radiation exposure for screened participants. Analysis of the NLST data estimated an average total radiation dose at 8 mSv per participant over three years, also including both screening and diagnostic examinations averaged over the entire screened population.⁸⁹ Participants in the ITALUNG trial had a mean effective dose^e between 6.2 and 6.8 mSv milliSieverts (mSv) over four years, including four annual LDCT examinations and related further investigations.^{58, 92} In the NELSON trial, the effective radiation dose per screening round was less

than 2 mSv, calculated for the volume computed tomography dose index (CTDIvol) at 0.8, 1.6, and 3.2 milliGrays (mGy), depending on the subject's body weight.^{10, 93, 94}

Since the first lung cancer screening trials were performed, technical improvements of hardware and software have resulted in a reduction in effective radiation dose.^{95, 96} Several European societies involved in lung cancer screening have issued recommendations with technical standards for future lung cancer screening programmes. The European Society of Thoracic Imaging (ESTI) advises the use of at least a 32-row CT scanner and a Volume Computed Tomography Dose Index (CTDIvol) of 0.4 mGy, 0.8 mGy and 1.6 mGy for participants <50 kg, 50–80 kg and >80 kg respectively.⁹⁷ More recently, a technical standard developed by the European Respiratory Society (ERS) recommends the CTDIvol must be kept as low as possible with the effective radiation dose well below 2 mSv.⁹⁸

For information, the estimated average exposure to ionizing radiation in Belgium (both background radiation as from artificial sources) is 4 mSv per year, of which 2.4 mSv per year is estimated to be from natural radiation sources.⁹⁹ In other words, the recommended effective radiation dose of a single screening LDCT is lower than ambient annual background radiation.

Radiation-related risk assessment

To be interpretable for the balance between benefits and harms of lung cancer screening, the risk of radiation-induced cancers (referred to as the lifetime attributable risk, LAR) can be estimated through modelling studies.

^e Of note, the effective dose is not measured but is a theoretical calculated dose based on the organs exposed by the applied radiation multiplied by tissue-weighting factors.⁹⁰ The definitions of different dose quantities are the following:

- Absorbed dose: the amount of energy deposited by radiation in a mass, expressed in milligrays (mGy);

- Equivalent dose: calculated for individual organs, expressed in millisieverts (mSv) to an organ;

- Effective dose: calculated for the whole body, expressed in mSv.⁹¹



It should be noted that various aspects of analyzing and modelling low-dose radiation risks are still subject of scientific debate (see Box 1). However, it is important to consider the radiation-related risk as only a small portion of screening participants will benefit from the examinations, while all participants will be subjected to the risks associated with the ionising radiation.^{100, 101}

Box 1 – Radiation risk assessment of low-dose exposure

While the secondary effects of high radiation doses are well known, there remains scientific debate regarding the risks related to low-dose exposure such as that used for diagnostic radiology procedures.

In short, the cancer risk from low-level radiation is mainly derived from large epidemiological studies comparing persons who were exposed to ionizing radiation (such as atomic bomb survivors,¹⁰² or cohorts of nuclear workers monitored with radiation badges¹⁰³) and appropriate control groups of non-exposed or low-exposed persons. By means of these epidemiological studies, however, significant increases in cancer risk can only be detected at dose levels that are much higher than the radiation doses used in medical imaging procedures (in this case LDCT screening). As there is no reliable information on the dose–effect relation for the low-dose range, one has to rely on an **extrapolation** of the effects observed in the higher dose range.¹⁰¹

The often-cited major US review of the evidence for cancer risks from low-dose exposures in 2006, the National Academy of Sciences Biologic Effects of Ionizing Radiation (BEIR) VII report, concluded that “the available scientific evidence is consistent with a linear dose-response relationship between ionizing radiation and the development of cancer in humans”. As such, a **linear no-threshold (LNT) hypothesis** is assumed which implies there is no threshold below which radiation-related risk of cancer disappears.¹⁰⁴

Since the publication of the BEIR VII report, many subsequent publications support excess cancer risks from low-dose ionizing radiation.¹⁰⁵⁻¹⁰⁷ A recent major update of cancer risk in a large cohort of nuclear workers (the INWORKS study) who are persistently exposed to

low doses of ionizing radiation supports a linear association between protracted low dose radiation and solid cancer mortality.¹⁰³

While the validity of using the LNT model for evaluating the carcinogenic risk of low doses exposure remains part of scientific debate, it is the most widely applied model for **radiation risk assessment** and recommended by advisory bodies such as the International Commission on Radiological Protection (ICRP) and the International Atomic Energy Agency (IAEA). According to the ICRP, the LNT model represents “the best practical approach to managing risk from radiation exposure and commensurate with the ‘**precautionary principle**’”, thereby indicating it’s intended for the purposes of radiation protection and not for quantifying individual radiation risks.¹⁰⁸

Based on the **ITALUNG** effective doses, the trial authors estimated this would result in a LAR of 1.2 per 10 000 male participants and 3.3 per 10 000 female participants after four screening rounds.^{58, 92} However, the use of nominal risk coefficients (sex-averaged and age-at-exposure-averaged) of the ICRP were used instead of population-specific risk coefficients.¹⁰¹

Using data from the often-cited Continuous Observation of Smoking Subjects study (**COSMOS**), a non-randomized screening study among 5 203 high-risk participants aged 50 and older, the LAR of cancer incidence after 10 years of annual screening were approximately 4 per 10 000 for men and 8 per 10 000 for women, when starting screening at age 50-54. Notably, the LAR for cancer was about threefold higher in women aged 50-54 than in men aged 65 and older. One radiation induced cancer would be expected in every 108 lung cancers detected after 10 years screening. The authors concluded that radiation exposure and cancer risk from LDCT screening for lung cancer, even if non-negligible, can be considered acceptable in light of the substantial mortality reduction associated with screening.¹⁰⁰



The **German Federal Office for Radiation Protection** published conservative^f estimates of the lifetime attributable cancer risks resulting from repeated LDCT screening tests for a German population of heavy smokers or ex-smokers, for different screening scenarios. For the estimation of the age-, sex-, and organ-specific LAR, German baseline rates for cancer incidence and cancer mortality were used. For the LAR related to lung cancer screening, it was assumed that the baseline rates for lung cancer in male and female heavy smokers are the same and that these are twice as high as the lung cancer rate of the average male population with mixed smoking habits (based on data from two large observational studies. The study results were calculated for a LDCT protocol with CTDIvol = 1 mGy.¹⁰¹

Considering a screening scenario with annual LDCT screening of (ex-)smokers aged between 50 and 75 years, the estimated radiation-related lifetime attributable risk to develop cancer **is below 0.25% for women** (25 per 10 000) and about **0.1% for men** (10 per 10 000) (Figure 14). Again, it is remarkable that the risk for radiation-induced (lung) cancer is significantly higher for women than for men. When assuming a mortality reduction of about 20% (cf. the results on lung cancer-related mortality above) and taking

only radiation risks into account, this screening scenario would result in a benefit–risk ratio of about 10 for women and about 25 for men.¹⁰¹ It should be noted that the mortality benefit of prolonged screening might be higher, so this benefit-risk estimate should be interpreted with caution. The study authors state that the risk values can be considered representative for a Western European population. Moreover, several of the presented results can very easily be adjusted to any CT protocol and scanner via the CTDIvol. The authors acknowledge their estimates are mostly conservative, for example by using a DDREF of 1 and by assuming that screening will be performed annually for the full screening period.

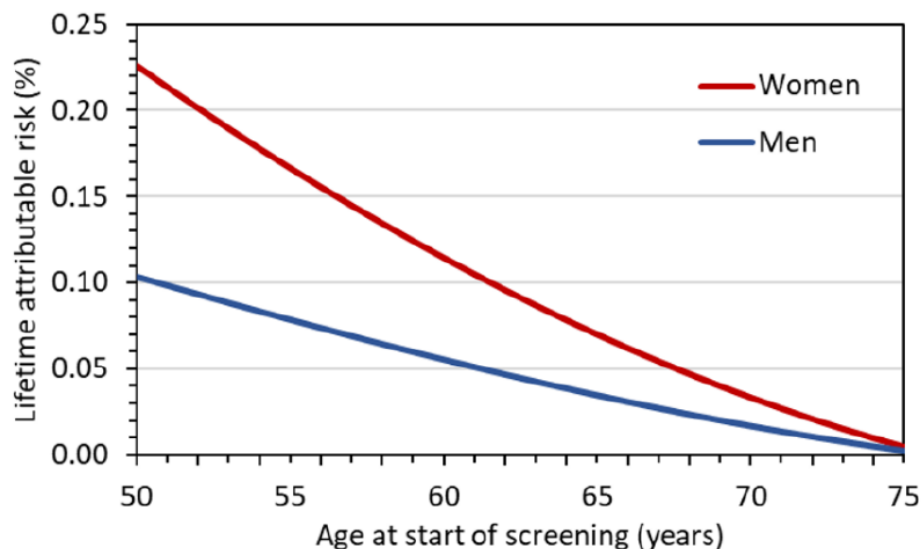
Of note, before medical radiological procedures (such as a LDCT scan) can be conducted as part of a population screening program, a justification study must be performed according to the model and modalities determined by **the Federal Agency for Nuclear Control (FANC)**, the regulatory body for nuclear safety and radiation protection in Belgium, as stipulated in the Belgian Royal Decree of 13 February 2020 on the medical exposures and exposures in non-medical imaging with medical radiological equipment.¹¹⁰

^f This conservative approach is reflected by not applying a risk coefficient of low doses (dose and dose-rate effectiveness factor, DDREF). The German Federal Office for Radiation Protection adopted a critical stance to the

DDREF concept, not in the least due to its design, and called for the DDREF to be abolished, i.e., a DDREF of 1, instead what ICRP recommends namely a DDREF of 2.¹⁰⁹ In the beforementioned COSMOS study, a DDREF of 1.5 was applied.



Figure 14 – Lifetime attributable cancer risks resulting from annual LDCT screening as a function of age at first screening, estimated by the German Federal Office for Radiation Protection



Source: Nekolla et al. (2022)¹⁰¹

Key points

- Only few included trials estimated cumulative radiation exposure for screened participants. This limited evidence does not allow to draw conclusions concerning harm from radiation exposure.
- The risk of radiation-induced cancers is estimated through modelling studies, and the most widely applied model for radiation risk assessment is the linear no-threshold model.

- The German Federal Office for Radiation Protection published conservative estimates of the lifetime attributable cancer risks resulting from repeated LDCT screening tests for a German population of heavy smokers or ex-smokers, considered representative for a Western European population. Considering a screening scenario with annual LDCT screening of (ex-)smokers aged between 50 and 75 years, the estimated radiation-related lifetime attributable risk to develop cancer is below 0.25% for women (25 per 10 000) and about 0.1% for men (10 per 10 000).



4. SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS OF LUNG CANCER SCREENING

4.1. Methods

4.1.1. Research questions

This chapter aims to systematically review the existing evidence on the cost-effectiveness and cost-utility of lung cancer screening using LDCT versus no screening (i.e., standard of care in Belgium) in an adult high-risk population. The purpose of this review is twofold. First, to check whether one or more health economic evaluations can be identified that can be transposed to or are performed in the Belgian health care context. In this case, conducting a primary analysis ourselves may not be required. Second, by systematically reviewing the literature, the methodological approaches taken by other evaluations (e.g., handling of false positives) as well as the chosen inputs (e.g., on QoL) can provide input for our own economic evaluation when no high-quality study for Belgium could be retrieved in the first step. The following research questions will be examined throughout this chapter:

- To what extent is a lung cancer screening programme deemed cost-effective in the health economic literature?
- To what extent are the relevant factors of lung cancer screening taken into account by the published health economic literature?

To answer the abovementioned research questions, a systematic literature search was conducted.

4.1.2. Search strategy

The systematic literature search was performed in two stages:

- First, existing Health Technology Assessments (HTAs) related to lung cancer screening were searched using the websites of HTA institutes,

which are members of the International Network of Agencies for Health Technology Assessment (INAHTA). An overview of the included HTA institutes can be consulted in Appendix 1, Table 94. This search was completed in October 2022.

- Second, a systematic literature review was conducted to retrieve full economic evaluations and reviews of economic evaluations in the following databases: EMBASE, Medline (Ovid), PsycInfo (Ovid), and EconLit (Ovid). The search for the systematic review was completed in January 2023.

Since the first stage HTA search identified two recent HTAs performing a systematic review of academic publications up to 2020 (i.e., AIHTA¹¹¹ and UK NSC¹¹²) and the clinical importance of the NELSON study, the second stage systematic literature review was limited to academic publications between 2020 and 10 January 2023 (day of the systematic search). The search strategy is based on various search strategies previously used in systematic reviews on the topic (such as Grover et al.,¹¹³ Peters et al.,¹¹⁴ and Snowsill et al.¹¹⁵) and can be found in Appendix 3.

4.1.3. Inclusion & exclusion criteria

The identified economic evaluations were assessed for eligibility using pre-defined inclusion and exclusion criteria. These criteria are based on the PICO defined in Chapter 3. Table 14 provides an overview of the inclusion and exclusion criteria used in the screening process. The population was restricted to an adult population at high risk of developing lung cancer due to current or previous smoking. As the main focus of this report lies on screening for lung cancer, studies examining patients with diagnosed or suspected lung cancer were excluded. In addition, studies focusing on a broader screening population (e.g., the general population) or on a population at low risk for lung cancer (e.g., never-smokers) were excluded. However, studies examining a sub-population of individuals at high risk for lung cancer (e.g., only men, only current smokers, etc.) were included. Studies were relevant when they compared an LDCT lung cancer screening programme to a situation without a lung cancer screening programme, which is currently the standard of care in Belgium.

**Table 14 – Inclusion & exclusion criteria for systematic literature review**

Criterion	Include	Exclude
Population	- Adults (age 18y and older) without diagnosed or suspected lung cancer at increased risk of lung cancer - Risk factors: current or previous tobacco smoking - Sub-populations: - Gender (only men, only women,...) - Smoking history (only current smokers, only former smokers,...)	- Patients with diagnosed or suspected lung cancer - People not at high risk of lung cancer: e.g., never-smokers, general population,...
Intervention	- Any lung cancer screening programme (e.g., various screening intervals, various implementations of screening programme,...) - Low-dose chest computer tomography (LDCT) - Screening programmes combined with or without smoking cessation initiatives	- Screening with any other imaging technology (e.g., magnetic resonance imaging, chest x-ray,...) - LDCT as a second line diagnostic - Screening for a combination of conditions (e.g., cardiovascular diseases and lung cancer) - Stand-alone smoking cessation programmes - LDCT combined with other interventions (e.g., diagnostic biomarkers, artificial intelligence,...)
Comparator	- No screening - Other screening strategy	- No comparator - Any other imaging or non-imaging screening (e.g., magnetic resonance imaging,...)
Study type	- Full economic evaluations: - Cost-effectiveness analysis (CEA) - Cost-utility analysis (CUA) - Cost-consequence analysis (CCA) - Cost-minimisation analysis (CMA) - Cost-benefit analysis (CBA)	- Budget impact analysis - Cost analysis - Financial analysis, return of investment analysis, profitability analysis - Non-incremental or comparative studies
Study design	- Model-based studies - Trial-based studies - Systematic reviews of relevant studies	- Descriptive studies - Implementation studies
Perspective	- Health care payer - Societal - Hospital	Other perspectives
Period	- Studies published since 2020 - No time restriction on Health Technology Assessments (HTAs) - No time restrictions on Belgian and Dutch studies	Studies published before 2020



Criterion	Include	Exclude
Type of publication	• Peer-reviewed journal articles • Health technology assesment (HTA)-reports	• Editorials, notes, letters, opinions, discussions • Conference abstracts • Not peer-reviewed
Language	• English, Dutch, and French	• Studies published in any other language

Studies comparing lung cancer screening strategies were also withheld as their results may deliver additional information on which screening strategy is to be preferred from a health economic point of view. Screening programmes consisting of screening and smoking cessation interventions were also included. However, stand-alone smoking cessation interventions were excluded. Any type of trial-based or model-based economic evaluation or review of full economic evaluations were included. In contrast, financial, non-incremental, and implementation studies were out of scope. Studies performed from the health care payer, societal, or hospital perspective were included, while studies examining costs from any other perspective were excluded. As mentioned before, only studies published from 2020 onwards were included due to the existing body of systematic reviews summarizing the evidence on the topic up to 2020. An exception is put in place for Belgian and Dutch studies, for which no time restrictions were imposed due to their comparability to the scope of this study and data relevance. To answer the second research question, HTAs published before 2020 were retained. Studies had to be published in a peer-reviewed journal or had to be published by an HTA institute from the list in Appendix 1 Table 94. Only studies published in English, Dutch, and French were withheld in the selection process.

4.1.4. Quantity of research available

The first stage identified 39 potentially relevant HTAs. After scanning the title and abstract, 7 HTAs were retained. After evaluating the full HTA reports, 6 HTAs were included in the final report:

- UK NSC, 2022a¹¹²;
- UK NSC, 2022b¹¹⁶;

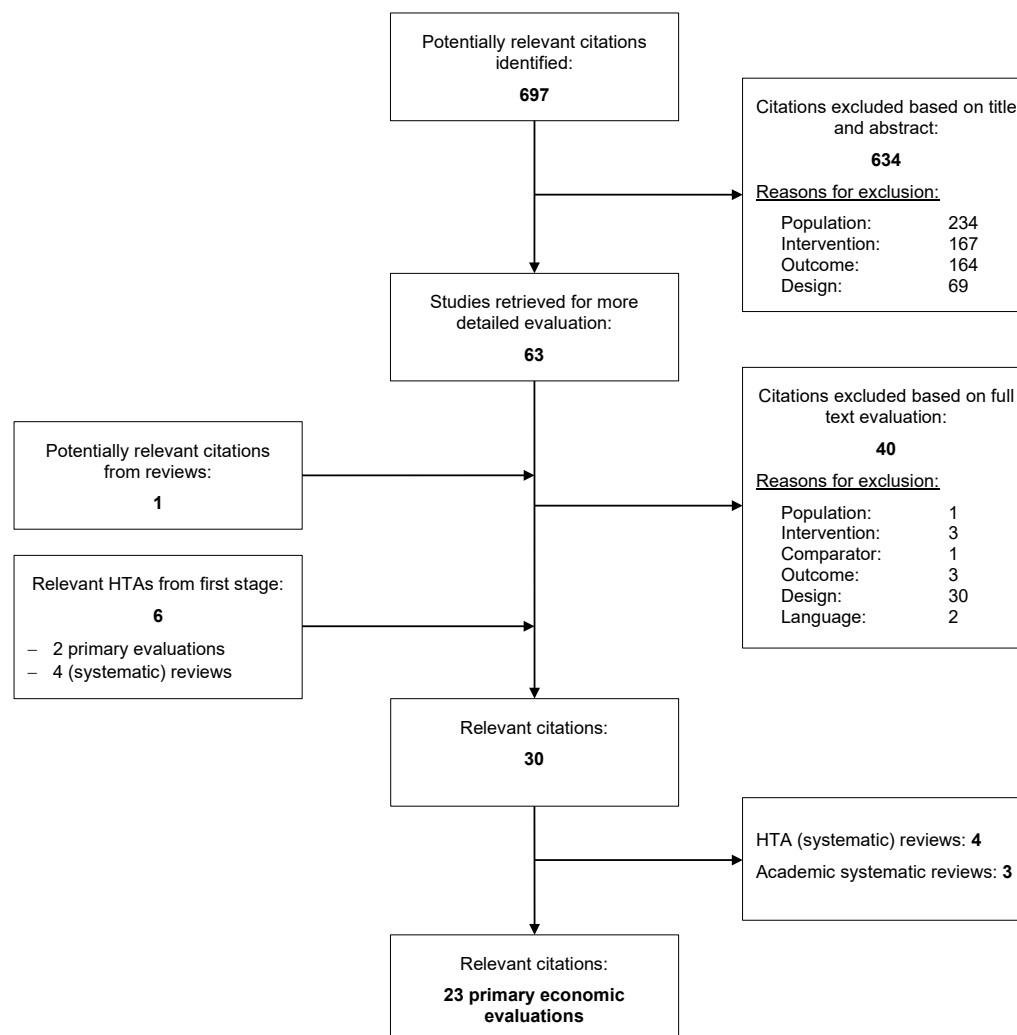
- AIHTA, 2020¹¹¹;
- MAHTAS, *year of publication unknown but search strategy dates back to 2017*¹¹⁷;
- IHE, 2014¹¹⁸;
- SBU, 2002¹¹⁹.

Appendix 1 Table 95 and Table 96 provides more information on the included & excluded HTAs.

In the second stage, the search strategy identified 3217 potentially relevant citations of which 534 were duplicates. Of the remaining 2683 citations, 1986 were published before 2020, resulting in 697 citations to be reviewed based on title and abstract. The remainder of the selection process was based on the previously discussed inclusion & exclusion criteria and is depicted in Figure 15 using the PRISMA flowchart standards. In the first round, 634 citations were excluded based on title and abstract and 63 were retained for full text evaluation. In addition, we identified one potentially relevant citation from a recent systematic review of Fabbro et al.¹²⁰ which was not identified by our search strategy (i.e., Du et al.¹²¹). After full text evaluation, 24 studies were retained for final inclusion in this report in the second stage. When adding the 6 relevant HTAs, previously identified in the first stage, the total number of relevant citations equals 30 studies. As this report aims to provide an update of the existing systematic reviews on the topic, our focus is primarily on the primary economic evaluations. As shown in the first two horizontal panels of Table 15, of the 30 relevant studies, 4 were HTA reports performing a (systematic review) and 3 were academic systematic reviews. In the remainder of this chapter, the 23 remaining primary economic evaluations will be discussed and evaluated.



Figure 15 – Flow chart of the second stage (2020-2023)



HTA: health technology assessment


Table 15 – Relevant citations & systematic reviews for search strategy performance check

Study ID (first author, year)	Full reference	Type of article
Stage I: Health Technology Assessments		
UK NSC, 2022a ¹¹²	UK NSC. Targeted screening for lung cancer in individuals at increased risk. London: UK National Screening Committee; 2022.	HTA: systematic review
UK NSC, 2022b ¹¹⁶	UK NSC. Interim report on the cost-effectiveness of low dose computed tomography (LDCT) screening for lung cancer in high risk individuals. London: UK National Screening Committee; 2022.	HTA: economic evaluation
AIHTA, 2020 ¹¹¹	Austrian Institute for Health Technology Assessment (AIHTA). Lung cancer screening in risk groups: A review-update of the economic evidence. In: Christian Ernst Heinrich Boehler, Wolf S, editors. Vienna; 2020.	HTA: systematic review
MaHTAS, xxxx ¹¹⁷	MaHTAS. Low Dose Computed Tomography for Lung Cancer Screening. Putrajaya, Malaysia: Malaysian Health Technology Assessment Section; xxxx.	HTA: systematic review
IHE, 2014 ¹¹⁸	IHE. Low dose computed tomography for the screening of lung cancer in adults. Edmonton, Alberta, Canada: The Institute of Health Economics; 2014.	HTA: systematic review & economic evaluation
SBU, 2002 ¹¹⁹	SBU. Computed tomography in screening for lung cancer. Sweden: Swedish Council on Technology Assessment in Health Care; 2002.	HTA: systematic review
Stage II: Academic publications		
Behar Harpaz, 2023 ¹²²	Behar Harpaz S, Weber MF, Wade S, Ngo PJ, Vaneckova P, Sarich PEA, et al. Updated cost-effectiveness analysis of lung cancer screening for Australia, capturing differences in the health economic impact of NELSON and NLST outcomes. British Journal of Cancer. 2023;128(1):91-101.	Economic evaluation
Al Khayat, 2022 ¹²³	Al Khayat MNMT, Eijssink JFH, Postma MJ, van de Garde EMW, van Hulst M. Cost-effectiveness of screening smokers and ex-smokers for lung cancer in the Netherlands in different age groups. European Journal of Health Economics. 2022;23(7):1221-7.	Economic evaluation
Cressman, 2022 ¹²⁴	Cressman S, Weber MF, Ngo PJ, Wade S, Behar Harpaz S, Caruana M, et al. Economic impact of using risk models for eligibility selection to the International lung screening Trial. Lung cancer (Amsterdam, Netherlands). 2022;176:38-45.	Economic evaluation
Fabbro, 2022 ¹²⁰	Fabbro M, Hahn K, Novaes O, Ó'Grálaigh M, O'Mahony JF. Cost-Effectiveness Analyses of Lung Cancer Screening Using Low-Dose Computed Tomography: A Systematic Review Assessing Strategy Comparison and Risk Stratification. Pharmacoeconomics - Open. 2022;6(6):773-86.	Systematic review
Gomez-Carballo, 2022 ¹²⁵	Gómez-Carballo N, Fernández-Soberón S, Rejas-Gutiérrez J. Cost-effectiveness analysis of a lung cancer screening programme in Spain. European Journal of Cancer Prevention. 2022;31(3):235-44.	Economic evaluation
Grover, 2022 ¹¹³	Grover H, King W, Bhattarai N, Moloney E, Sharp L, Fuller L. Systematic review of the cost-effectiveness of screening for lung cancer with low dose computed tomography. Lung Cancer. 2022;170:20-33.	Systematic review
Kim, 2022 ¹²⁶	Kim J, Cho B, Kim SH, Choi CM, Kim Y, Jo MW. Cost Utility Analysis of a Pilot Study for the Korean Lung Cancer Screening Project. Cancer Research and Treatment. 2022;54(3):728-36.	Economic evaluation



Study ID (first author, year)	Full reference	Type of article
Nagy, 2022 ¹²⁷	Nagy B, Szilberhorn L, Gyorbiro DM, Moizs M, Bajzik G, Kerpel-Fronius A, et al. Shall We Screen Lung Cancer With Low-Dose Computed Tomography? Cost-Effectiveness in Hungary. <i>Value in Health Regional Issues</i> . 2022;34:55-64.	Economic evaluation
Peters, 2022 ¹¹⁴	Peters JL, Snowsill TM, Griffin E, Robinson S, Hyde CJ. Variation in Model-Based Economic Evaluations of Low-Dose Computed Tomography Screening for Lung Cancer: A Methodological Review. <i>Value in Health</i> . 2022;25(4):656-65.	Systematic review
Yuan, 2022a ¹²⁸	Yuan J, Sun Y, Wang K, Wang Z, Li D, Fan M, et al. Cost Effectiveness of Lung Cancer Screening With Low-Dose CT in Heavy Smokers in China. <i>Cancer Prevention Research</i> . 2022;15(1):37-44.	Economic evaluation
Yuan, 2022b ¹²⁹	Yuan J, Sun Y, Xu F, Li M, Fan M, Zhang C, et al. Cost-effectiveness of lung cancer screening combined with nurse-led smoking cessation intervention: A population-based microsimulation study. <i>International journal of nursing studies</i> . 2022;134:104319.	Economic evaluation
Zeng, 2022 ¹³⁰	Zeng X, Zhou Z, Luo X, Liu Q. Lung cancer screening with low-dose computed tomography: National expenditures and cost-effectiveness. <i>Frontiers in public health</i> . 2022;10:977550.	Economic evaluation
Zhao, 2022 ¹³¹	Zhao Z, Du L, Li Y, Wang L, Wang Y, Yang Y, et al. Cost-Effectiveness of Lung Cancer Screening Using Low-Dose Computed Tomography Based on Start Age and Interval in China: Modeling Study. <i>JMIR public health and surveillance</i> . 2022;8(7):e36425.	Economic evaluation
Cadham, 2021 ¹³²	Cadham CJ, Cao P, Jayasekera J, Taylor KL, Levy DT, Jeon J, et al. Cost-Effectiveness of Smoking Cessation Interventions in the Lung Cancer Screening Setting: A Simulation Study. <i>Journal of the National Cancer Institute</i> . 2021;113(8):1065-73.	Economic evaluation
Diaz, 2021 ¹³³	Diaz M, Garcia M, Vidal C, Santiago A, Gnutti G, Gómez D, et al. Health and economic impact at a population level of both primary and secondary preventive lung cancer interventions: A model-based cost-effectiveness analysis. <i>Lung Cancer</i> . 2021;159:153-61.	Economic evaluation
Esmaili, 2021 ¹³⁴	Esmaili MH, Seyednejad F, Mahboub-Ahari A, Ameri H, Abdollahzad H, Safaei N, et al. Cost-effectiveness analysis of lung cancer screening with low-dose computed tomography in an Iranian high-risk population. <i>Journal of medical screening</i> . 2021;28(4):494-501.	Economic evaluation
Sun, 2021 ¹³⁵	Sun C, Zhang X, Guo S, Liu Y, Zhou L, Shi J, et al. Determining cost-effectiveness of lung cancer screening in urban Chinese populations using a state-transition Markov model. <i>BMJ Open</i> . 2021;11(7).	Economic evaluation
Toumazis, 2021 ¹³⁶	Toumazis I, De Nijs K, Cao P, Bastani M, Munshi V, Ten Haaf K, et al. Cost-effectiveness Evaluation of the 2021 US Preventive Services Task Force Recommendation for Lung Cancer Screening. <i>JAMA Oncology</i> . 2021;7(12):1833-42.	Economic evaluation
Du, 2020 ¹³⁷	Du Y, Sidorenkov G, Heuvelmans MA, Groen HJM, Vermeulen KM, Greuter MJW, et al. Cost-effectiveness of lung cancer screening with low-dose computed tomography in heavy smokers: a microsimulation modelling study. <i>European Journal of Cancer</i> . 2020;135:121-9.	Economic evaluation
Evans, 2020 ¹³⁸	Evans WK, Gauvreau CL, Flanagan WM, Memon S, Yong JHE, Goffin JR, et al. Clinical impact and cost-effectiveness of integrating smoking cessation into lung cancer screening: a microsimulation model. <i>CMAJ open</i> . 2020;8(3):E585-E92.	Economic evaluation
Griffin, 2020 ¹³⁹	Griffin E, Hyde C, Long L, Varley-Campbell J, Coelho H, Robinson S, et al. Lung cancer screening by low-dose computed tomography: a cost-effectiveness analysis of alternative programmes in the UK using a newly developed natural history-based economic model. <i>Diagnostic and Prognostic Research</i> . 2020;4(1):20.	Economic evaluation



Study ID (first author, year)	Full reference	Type of article
Jaine, 2020 ¹⁴⁰	Jaine R, Kvizhinadze G, Nair N, Blakely T. Cost-effectiveness of a low-dose computed tomography screening programme for lung cancer in New Zealand. <i>Lung Cancer</i> . 2020;144:99-106.	Economic evaluation
McLeod, 2020 ¹⁴¹	McLeod M, Sandiford P, Kvizhinadze G, Bartholomew K, Crengle S. Impact of low-dose CT screening for lung cancer on ethnic health inequities in New Zealand: A cost-effectiveness analysis. <i>BMJ Open</i> . 2020;10(9).	Economic evaluation
Veronesi, 2020 ¹⁴²	Veronesi G, Navone N, Novellis P, Dieci E, Toschi L, Velutti L, et al. Favorable incremental cost-effectiveness ratio for lung cancer screening in Italy. <i>Lung Cancer</i> . 2020;143:73-9.	Economic evaluation
Academic systematic reviews published before 2020 (only used to control the performance of the search strategy)		
Snowsill, 2018 ¹¹⁵	Snowsill T, Yang H, Griffin E, Long L, Varley-Campbell J, Coelho H, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. <i>Health Technology Assessment (Winchester, England)</i> . 2018;22(69):1-276.	Systematic review
Azar, 2017 ¹⁴³	Azar FE, Azami-Aghdash S, Pournaghi-Azar F, Mazdaki A, Rezapour A, Ebrahimi P, et al. Cost-effectiveness of lung cancer screening and treatment methods: a systematic review of systematic reviews. <i>BMC Health Services Research</i> . 2017;17(1):413.	Systematic review
Raymakers, 2016 ¹⁴⁴	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. <i>Applied Health Economics & Health Policy</i> . 2016;14(4):409-18.	Systematic review
Puggina, 2016 ¹⁴⁵	Puggina A, Broumas A, Ricciardi W, Boccia S. Cost-effectiveness of screening for lung cancer with low-dose computed tomography: a systematic literature review. <i>European Journal of Public Health</i> . 2016;26(1):168-75.	Systematic review
Black, 2006 ¹⁴⁶	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. <i>Health Technology Assessment (Winchester, England)</i> . 2006;10(3):iii-iv, ix-x, 1-90.	Systematic review
Klittich, 2002 ¹⁴⁷	Klittich WS, Caro JJ. Lung Cancer Screening. <i>American Journal of Respiratory Medicine</i> . 2002;1(6):393-401.	Systematic review
Systematic reviews published after completion of search strategy (only used to control the performance of the search strategy)		
Behr, 2023 ¹⁴⁸	Behr CM, Oude Wolcherink MJ, Ijzerman MJ, Vliegenthart R, Koffijberg H. Population-Based Screening Using Low-Dose Chest Computed Tomography: A Systematic Review of Health Economic Evaluations. <i>PharmacoEconomics</i> . 2023;41(4):395-411.	Systematic review

Notes: UK NSC, 2022a and Peters, 2022 are updates of Snowsill, 2018. Abbreviations: HTA = Health Technology Assessment.



column of Table 16, the search strategy was able to identify all of the previously identified economic evaluations in systematic reviews and HTAs with the exception of Du et al.¹²¹, which was added from other reviews but excluded in the second round based on full text evaluation. The exclusion criteria for studies included by other systematic reviews but which were excluded in this report are available in 0.

[illegible]

[illegible]



	KCE, 2023	Behr, 2023 ¹⁴⁸	Grover, 2022 ¹¹³	Fabbro, 2022 ¹²⁰	Peters, 2022 ¹¹⁴	UK NSC, 2022a ¹¹²	AIHTA, 2020 ¹¹¹	Snowsill, 2018 ¹¹⁵	MaHTAS, xxxx ¹¹⁷	Azar, 2017 ¹⁴³	Raymakers, 2016 ¹⁴⁴	Puggina, 2016 ¹⁴⁵	Black, 2006 ¹⁴⁶	SBU, 2002 ¹¹⁹	Klittich, 2002 ¹⁴⁷
Ten Haaf, 2017 ¹⁶²	E	x	x	x	x	(x)	n.s.	x							
Treskova, 2017 ¹⁶³	E	x	x	x	x	(x)									
Yang, 2017 ¹⁶⁴	E		x		x	(x)	x								
<i>Raymakers, 2016¹⁴⁴</i>	E						x	x	x	x					
Evans, 2016 ¹⁶⁵	E	x	x												
Field, 2016a ⁸⁸	E	x	x		x	(x)	n.s.	x							
Field, 2016b ¹⁶⁶	E						n.s.	x							
Goffin, 2016 ¹⁶⁷	E	x	x	x	x	(x)	n.s.	x							
<i>Puggina, 2016¹⁴⁵</i>	E						x	x							
Black, 2015 ¹⁶⁸	E	x					n.s.	x							
Fitzgerald, 2015 ¹⁶⁹	E	x													
Goffin, 2015 ¹⁷⁰	E	x	x	x	x	(x)	n.s.	x							
Kanarkiewicz, 2015 ¹⁷¹	E	x	x						x						
Black, 2014 ¹⁷²	E	x	x		x	(x)	n.s.	x			x	x			
IHE, 2014 ¹¹⁸	E		x				x								
Pyenson, 2014 ¹⁷³	E	x	x	x	x	(x)	n.s.	x			x	x			
Tabata, 2014 ¹⁷⁴	E	x	x	x	x	(x)	n.s.	x							
Shmueli, 2013 ¹⁷⁵	E	x	x		x	(x)	n.s.	x			x	x			
Villanti, 2013 ¹⁷⁶	E		x	x	x	(x)		x			x	x			
Goulart, 2012 ¹⁷⁷	E		x		x	(x)	x	x							
Pyenson, 2012 ¹⁷⁸	E	x	x	x	x	(x)		x			x				
McMahon, 2011 ¹⁷⁹	E	x	x	x	x	(x)	n.s.	x			x	x			
Castleberry, 2009 ¹⁸⁰	E		x												
Whynes, 2008 ¹⁸¹	E		x	x	x	(x)	n.s.	x							
<i>Black, 2006¹⁴⁶</i>	E						x	x							



	KCE, 2023	Behr, 2023 ¹⁴⁸	Grover, 2022 ¹¹³	Fabbro, 2022 ¹²⁰	Peters, 2022 ¹¹⁴	UK NSC, 2022a ¹¹²	AIHTA, 2020 ¹¹¹	Snowsill, 2018 ¹¹⁵	MaHTAS, xxxx ¹¹⁷	Azar, 2017 ¹⁴³	Raymakers, 2016 ¹⁴⁴	Puggina, 2016 ¹⁴⁵	Black, 2006 ¹⁴⁶	SBU, 2002 ¹¹⁹	Klittich, 2002 ¹⁴⁷
<i>CADTH, 2006^{182, 183}</i>	E							x							
Beinfeld, 2005 ¹⁸⁴	E														
Manser, 2005 ¹⁸⁵	E		x	x	x	(x)	n.s.	x			x	x			
Mahadevia, 2003 ¹⁸⁶	E		x	x	x	(x)		x			x	x	x	x	
Wisnivesky, 2003 ¹⁸⁷	E		x		x	(x)		x	x			x	x		
Chirikos, 2002 ¹⁸⁸	E		x	x	x	(x)		x			x		x	x	
<i>Klittich, 2002¹⁴⁷</i>	E							x							
SBU, 2002	x														
Marshall, 2001a ¹⁸⁹	E		x	x	x	(x)		x			x	x	x	x	x
Marshall, 2001b ¹⁹⁰	E		x	x	x	(x)		x			x		x		x
Caro, 2000 ¹⁹¹	E														x
Okamoto, 2000 ¹⁹²	E										x		x		x
Baba, 1998 ¹⁹³	E														x
Eddy, 1989 ¹⁹⁴	E														x
Kaneko, 1996 ¹⁹⁵	E														x

Notes: 'E' means the publication was identified by our search strategy but was excluded based on the inclusion & exclusion criteria in Table 14. Studies in *Italic* in the first column are systematic reviews. CADTH, 2006 does not explicitly focus on lung cancer screening and is not retrievable. IHE, 2014 and UK NSC, 2022b did not perform a systematic literature review. UK NSC, 2022a refers to Peters, 2022 for the systematic review. References of Peters, 2022 are therefore indicated with (x) in the column of UK NSC, 2022a. AIHTA, 2020 conducted an update systematic review of previous systematic reviews and therefore excluded all studies already selected in the previous systematic reviews (n.s. refers to studies identified by the search strategy but not selected because they were already selected by previous reviews). * Jaine, 2020 is the corrected version of Jaine, 2018. *Griffin, 2020 is the academic publication of Snowsill, 2018.



4.1.5. Data extraction

An in-house developed data extraction sheet was used to extract the relevant information from the selected publications. The template of the data extraction sheet is available in Appendix 4. The information gathered in the data extraction sheets served as the basis for the summary tables in the report.

4.2. Overview of economic evaluations

As mentioned previously, our search strategy identified 23 primary economic evaluations of lung cancer screening (i.e., 2 HTAs and 21 peer-reviewed journal articles). This section provides a detailed overview of the selected primary economic evaluations by summarizing the general characteristics, the PICO (population, intervention, comparator, outcome), the model inputs in terms of costs and effects, the relevant (LCS) screening-factors considered in the evaluations, the results, and finally the conclusions. The resulting insights will be used to provide input for a context-specific economic evaluation and will be discussed in chapter 8.

4.2.1. General characteristics

Table 17 summarizes the general characteristics of the full health economic evaluations included in this chapter. The selected studies originate from a large variety of **countries**, including China (5), Canada (3), Australia (2), Spain (2), the United Kingdom (2), the Netherlands (2), the USA (2), and New-Zealand (2). The remaining studies were conducted in South Korea, Iran, Hungary, and Italy. Apart from the study of Du et al.¹³⁷ conducting solely a cost-effectiveness analysis (CEA), all included studies conducted cost-utility analyses (CUA). Veronesi et al.¹⁴², Behar Harpaz et al.¹²², and Gomez-Carballo et al.¹²⁵ conducted both a CEA and a CUA in their respective studies.

All the included studies rely on **health economic modelling** to assess incremental costs and health outcomes of an LDCT lung cancer screening programme. More specifically, ten studies developed a Markov model to model transitions between lung cancer-related health states over the respective time horizon used in the study, after which health outcomes and costs are assigned to each health state. In most studies, the health states corresponded to the stages of lung cancer (either I-IV or local-regional-distant) in addition to health states corresponding to death and healthy. Two studies (Esmaeili et al.¹³⁴ and Nagy et al.¹²⁷) reported using both a Markov model and a decision tree. Three out of the eleven Markov-based studies reported using a model based on the Markov principles. Cressman et al.¹²⁴ described their model as a 'semi-Markov model' as they relaxed the memoryless Markovian property and allowed time-dependent events (i.e., cancer incidence and increasing mortality rates with age) to change. Both McLeod et al.¹⁴¹ and Jaine et al.¹⁴⁰ developed a Markov-based macrosimulation stage shift model. In total, 5 of the 23 included studies used a decision tree in their analyses,^{116, 127, 134, 139, 142} of which two combined a decision tree with a discrete event simulation model (i.e., ENaBL)^{116, 139} and, as mentioned previously, two with a Markov model.^{127, 134} The former two studies simulated the progression of lung cancer using a natural history model. Next, the results were used as an input to the discrete event simulation model to simulate costs and effects of the screening and non-screening groups, respectively. Seven studies relied on a microsimulation framework with IHE¹¹⁸ using the Canadian Cancer Risk Management Model (CRMM) and Du et al.¹³⁷ the SiMRiSc model. Both Toumazis et al.¹³⁶ and Cadham et al.¹³² opted for one or more models of the Cancer Intervention and Surveillance Modelling Network (CISNET models) in their respective studies. Diaz et al.¹³³ on the other hand, opted for a hybrid Markov-based microsimulation model by developing a Markov model but microsimulating large parts of the model (categorized as microsimulation model). Finally, Behar-Harpaz et al.¹²² developed a deterministic, multi-cohort model.


Table 17 – Model characteristics of academic publications (2020-2023) & HTAs

	Country	Analytic technique	Type of model	Perspective	Time horizon	Discount rate costs	Discount rate benefits	Conflict of interest
Academic publications								
Behar Harpaz, 2023 ¹²²	Australia	CEA & CUA	Simplified, multi-cohort, deterministic model	Universal public payer	Lifetime horizon	5%	5%	No
Al Khayat, 2022 ¹²³	The Netherlands	CUA	Markov model	Health care payer	Lifetime horizon	4%	1.5%	No
Cressman, 2022 ¹²⁴	Australia & Canada	CUA	Semi-Markov model	Universal healthcare payer	Lifetime horizon	3%	3%	Yes
Gomez-Carballo, 2022 ¹²⁵	Spain	CEA & CUA	Markov model	National health system	Lifetime horizon	3%	3%	No
Kim, 2022 ¹²⁶	South Korea	CUA	Markov model	Limited social	Until death or 100y	5%	5%	No
Nagy, 2022 ¹²⁷	Hungary	CUA	Decision tree & Markov model	Not reported, but presumably health care payer	Lifetime horizon	3.7%	3.7%	No*
Yuan, 2022a ¹²⁸	China	CUA	Markov model	Health care payer	50y (until death or 90y)	3%	3%	No
Yuan, 2022b ¹²⁹	China	CUA	Microsimulation model (interpreted as Markov model)	Health care payer	45y (until death or 90y)	3%	3%	No
Zeng, 2022 ¹³⁰	China	CUA	Markov model	Health care payer	Not reported	5%	5%	No
Zhao, 2022 ¹³¹	China	CUA	Markov model	Societal	Lifetime horizon	5%	5%	No
Cadham, 2021 ¹³²	The United States of America (USA)	CUA	Microsimulation model (CISNET)	Societal	Lifetime horizon	3%	3%	Yes
Diaz, 2021 ¹³³	Spain	CUA	Markov-based microsimulation model	Societal	45y (until death or 80y)	3%	3%	No



	Country	Analytic technique	Type of model	Perspective	Time horizon	Discount rate costs	Discount rate benefits	Conflict of interest
Esmaeili, 2021 ¹³⁴	Iran	CUA	Markov model & decision tree	Health care payer	Not reported	3.5%	3.5%	No
Sun, 2021 ¹³⁵	China	CUA	Markov model	"Sociological perspective"	Until 76y	3%	3%	No
Toumazis, 2021 ¹³⁶	The United States of America (USA)	CUA	Microsimulation model (4 CISNET models)	Health care payer	Until death or 90y	3%	3%	Yes
Du, 2020 ¹³⁷	The Netherlands	CEA	Microsimulation model (SiMRiSc)	Health insurance	Lifetime horizon	4%	1.5%	No
Evans, 2020 ¹³⁸	Canada	CUA	Microsimulation model	Health care payer	Lifetime horizon	1.5%	1.5%	No
Griffin, 2020 ¹³⁹	The United Kingdom (UK)	CUA	ENaBL & decision tree	NHS & personal social services	Lifetime horizon	3.5%	3.5%	No
Jaine, 2020 ¹⁴⁰	New Zealand	CUA	Markov-based macrosimulation stage shift model	Health care payer	Lifetime horizon	3%	3%	Not reported
McLeod, 2020 ¹⁴¹	New Zealand	CUA	Markov-based macrosimulation model	Health care payer	Lifetime horizon	3%	3%	No*
Veronesi, 2020 ¹⁴²	Italy	CUA & CEA	Decision tree	Health care payer ("Tax payer")	5y	3%	Not reported	Yes
Health Technology Assessments (HTAs)								
UK NSC, 2022b ¹¹⁶	The United Kingdom (UK)	CUA	ENaBL & decision tree	NHS & personal social services	Lifetime horizon	3.5%	3.5%	Not reported
IHE, 2014 ¹¹⁸	Canada	CUA	CRMM & microsimulation model	Health care payer ("Canadian payer")	25y	3%	3%	No

Notes: *Studies declared potential conflict of interest, but was related to public funding not affecting the study design, methods, and results. CEA = Cost-Effectiveness Analysis, CUA = Cost-Utility Analysis, ENaBL = Exeter NATural history-Based economic model of Lung cancer screening, CISNET = Cancer Intervention and Surveillance Modeling Network, CRMM = Canadian Cancer Risk Management Model, NHS = National Health Service



The **perspective** out of which the various studies have been performed is an important characteristic to consider as the chosen perspective determines to a large extent which costs were taken into account by the respective studies. A large majority of studies (16 studies) carried out their analyses from the health care payer perspective, meaning these studies included all costs arising from the provision of health care within the entire health care system. In contrast, Du et al.¹³⁷ only performed the analyses from a health insurance perspective. A societal perspective is the broadest perspective one can take as this perspective implies taking into account not only the direct medical costs, but additionally the direct and indirect non-medical costs, such as productivity loss, transportation costs, etc. Five studies claim performing their analyses from a societal perspective.^{126, 131, 132, 135} However, none of the studies included all of the costs for society as a whole. Kim et al.,¹²⁶ for example, only included transportation costs, patient time, caregiver time, and direct medical costs but did not take absence at work or productivity loss into account. Nagy et al.¹²⁷ did not report the perspective used in the analyses. Based on the included costs in the respective study, a health care payer perspective could be assumed.

In addition to the perspective, the **time horizon** over which the health economic evaluations are performed determines to which extent future costs and health outcomes are taken into account in the analyses and can therefore have a major impact on the results. Thirteen studies modelled costs and health outcomes of a lung cancer screening programme over a lifetime horizon. Five studies used a hybrid format by modelling until death or until the patient reaches a specific age (i.e., 80, 90, or 100 years).^{126, 128, 129, 133, 136} IHE et al.¹¹⁸ applied a time horizon of 25 years, Veronesi et al.¹⁴² modelled a 5 years' time horizon, and Sun et al.¹³⁵ modelled until participants reached the age of 76 years. Finally, the time horizons modelled by Zeng et al.¹³⁰ and Esmaeili et al.¹³⁴ remain unclear. Interestingly, only three studies employing a lifetime horizon in the base case analyses varied the time horizon in the sensitivity analyses of which the impact will be discussed in Section 4.3.2.^{116, 122, 125}

In terms of **discount rate**, about half the studies (11 studies) discounted both the future costs and health outcomes at a rate of 3%. Seven studies used a more elevated discount rate for future costs and health outcomes,

meaning future costs and health outcomes reduce in weight compared to a lower discount rate. Of these seven studies, four applied a discount rate of 5%,^{122, 126, 130, 131} three a rate of 3.5%,^{116, 134, 139} and one a rate of 3.7%.¹²⁷ Only the study of Evans et al.¹³⁸ used a lower discount rate of 1.5% for both future costs and health outcomes. Al Khayat et al.¹²³ and Du et al.¹³⁷ are the only studies discounting future costs and health outcomes at a different discount rate with rates of 4% for the costs and 1.5% for the health outcomes, which is in line with the Dutch guidelines on health economic evaluations. Two studies were insufficiently clear on the discount rates employed in their analyses. Whilst Veronesi et al.¹⁴² only reported a discount rate for the future costs (i.e., 3%), the authors did not report a discount rate for the future health outcomes, which could lead to the assumption that they did not discount future health outcomes. Important to note is that approximately half of the studies (11 studies) varied the specified discount rates in the sensitivity analyses.^{116, 124-126, 128-131, 139-141}

Finally, all but two studies (Jaine et al.¹⁴⁰ & UK NSC¹¹⁶) provided **conflicts of interest statements**. Four studies disclosed detailed potential conflicts of interest for each author.^{124, 127, 132, 136, 141, 142} The remaining studies (17) provided a statement that no conflicts of interest were present. The full conflicts of interest statements of the included studies are summarized in Appendix 5.

Key points

- High variability in geographical origin of the studies can be observed.
- The large majority of included studies opted for cost-utility analysis by means of either a Markov model or a microsimulation model.
- Analyses were mainly carried out from a health care payer perspective. Rarely chosen alternatives include the hospital or (limited) societal perspective.
- While most studies used a lifetime horizon in their analyses, a selection of studies modelled costs and health outcomes for



considerably shorter time horizons (e.g., 5y, 25y). The time horizon was rarely varied in the sensitivity analyses.

- The majority of studies opted for constant discounting of costs and health outcomes at a rate of 3%. In line with their national guidelines, only two studies discounted costs and health outcomes at different discount rates. Most studies varied the discount rate in the sensitivity analyses.
- Conflicts of interest statements were provided by all but two studies.

4.2.2. Population, intervention, comparator, and outcome characteristics

An overview of the general characteristics of the selected studies is provided in Table 18. The following paragraphs discuss the population eligible for screening, the interventions, comparators, and outcomes used by the selected studies in their primary economic evaluations.

4.2.2.1. Population

As formulated in the inclusion & exclusion criteria, this study focuses on screening for lung cancer in a population at high risk for lung cancer due to heavy current and/or former smoking. In general, the selected studies defined the high-risk population eligible for the screening programme using an age window, smoking history, and/or risk assessment tools. The large majority of studies (19 studies) used a combination of age and smoking history as eligibility criteria for the examined lung cancer screening programme. In contrast, the two UK-based studies used a combination of age and a pre-defined risk threshold calculated using a lung cancer-specific risk assessment tool (i.e., Liverpool Lung Project lung cancer risk prediction model, version 2 – LLPv2).^{116, 139} Zeng et al.¹³⁰ took a completely different approach by combining age criteria with the amount of lung cancers within this population based on Chinese lung cancer prevalence data. Cressman et al.¹²⁴ compared the use of a risk assessment tool (i.e., PLCO_{m2012}) to define the screening-eligible population with a combination of age and

smoking history. Finally, it is important to note that the study of Diaz et al.¹³³ only included male participants in the screening programme.

In terms of **start/stop ages** for screening, most studies used the age eligibility criterium of the NLST ranging between 55 and 74 (7 studies).^{118, 126, 127, 134, 138, 140, 141} The NELSON age criterium (50-74/75) was used by three studies^{125, 128, 137}, while five studies took a different approach and used an age range between 55 and 79 or 80.^{116, 124, 132, 139, 142} In addition to the above, Behar-Harpaz et al.¹²² compared both the NLST and NELSON eligibility criteria (including the age criteria) to a situation without screening. Likewise, Toumazis et al.¹³⁶ compared the USPSTF-2021 (50-80) to the USPSTF-2013 (55-80) eligibility criteria. While Zeng et al.¹³⁰ used a considerably lower start age of 30 combined with a stop age of 79, Diaz et al.¹³³ put forward a lower stop age of 65 with a start at 55. Four studies did not define base case age eligibility criteria for screening, but defined multiple screening start ages to be considered as one of the research questions of their study.^{123, 129-131} Interestingly, the majority of studies (13 studies) performed scenario analyses based on solely the age eligibility criterium, which will be discussed in the section aimed at the sensitivity analyses.

With regard to **smoking history**, most studies defined eligibility as at least 30 pack-years (PY) of smoking and either currently smoking or having quit a maximum of 15 years ago which corresponds to the NLST and USPSTF-2013 criteria (7 studies).^{124, 128, 132, 138, 140-142} In contrast, three studies relaxed this criterium by only looking at the amount of pack-years with a threshold of 30 pack-years.^{118, 126, 133} Only two studies employed the NELSON criteria for smoking history, which are defined as current smokers or having quit a maximum of 10 years combined with either at least 15 cigarettes/day for at least 25 years or at least 10 cigarettes/day for at least 30 years.^{123, 125}, of which Al Khayat et al.¹²³ claim following the NELSON criteria but actually used an integrated version of the criteria by defining the criterium as current smokers or having quit a maximum of 10 years combined with at least 15 cigarettes/day for at least 30 years. In line with the age criterium, Behar-Harpaz et al.¹²² compared both the NLST and NELSON eligibility criteria (including the smoking history criteria) to a situation without screening and Toumazis et al.¹³⁶ compared the USPSTF-2021 (20+PY, <15y since quitting) to the USPSTF-2013 (30+PY, <15y since quitting) eligibility criteria.



In contrast, Esmaeili et al.¹³⁴ took a different approach by using a considerably larger interval between 13 and 38 pack-years without defining a time since quitting. Finally, three studies only included current smokers in the eligible population for screening when they had been smoking at least 20 cigarettes/day¹³⁷, or had either an ongoing smoking history of 20^{131, 135} or 25PY¹²⁷. Of the studies using smoking history as a direct eligibility criterium for screening, four studies examined the impact of the smoking history requirements on the ICER to some degree.^{127, 129, 136, 140} However, this will be discussed further in the section focusing on the sensitivity analyses.

As an alternative to age and/or smoking history to define population eligibility criteria, a total of three studies used a pre-defined risk threshold resulting from an individual **risk assessment tool**.^{116, 124, 139} Two studies used the Liverpool Lung Project lung cancer risk prediction model, version 2 (LLPv2).^{116, 139} The LLPv2 takes age, sex, and smoking status into account to calculate the lung cancer risk. Both studies varied the threshold above which people were eligible for screening between a lung cancer risk of 3% and 5%. In addition to the risk assessment tool, both studies additionally used an age interval between 55 and 80. Cressman et al.¹²⁴ used the PLCO_{m2012} risk prediction tool to define screening eligibility, which employs age, education, smoking history, coexisting COPD, family history of lung cancer, and body mass index (BMI) as predictors for lung cancer risk. Within this study, people with a six-year lung cancer risk of $\geq 1.7\%$ were eligible for screening. All the studies using risk prediction tools varied the risk threshold defining screening eligibility in their sensitivity or scenario analyses to estimate its impact on the ICER.

4.2.2.2. *Intervention*

The intervention characteristics of the included studies are summarized in columns 4-6 of Table 18. In terms of **screening intervals**, reported in column 4 of Table 18, the included studies vary considerably. Nine studies assessed annual screening in the base case,^{123, 126, 128, 129, 132, 135, 136, 138, 142} but Veronesi et al.¹⁴² for only five years (i.e., five consecutive screens). Two studies employed a biennial screening interval in their base case of which Jaine et al.¹⁴⁰ limits the time horizon to twenty years (i.e., ten consecutive screens).^{140, 141} Esmaeili et al.¹³⁴ was the only study evaluating a triennial

screening interval in the base case, whilst Cressman et al.¹²⁴ followed the screening protocol of ILST resulting in a baseline screening and a follow-up screening round after two years. Two other studies followed the protocols of large lung cancer screening trials to a certain extent.^{122, 125} Behar Harpaz et al.¹²² compares the NLST screening strategy (0y, 1y, 2y) to the strategy used in the NELSON trial (0y, 1y, 3y, 5y). Gomez-Carballo et al.¹²⁵ on the other hand also followed the screening strategy of the NELSON trial, but eliminated the final screening round. The remaining eight studies defined various screening intervals in their base case as finding the optimal screening interval was one of the main research questions of the studies.^{116, 118, 127, 130, 131, 133, 137, 139} All eight studies included annual screening, seven additionally assessed biennial screening,^{116, 118, 127, 130, 133, 137, 139} five also assessed a one-off screening,^{116, 130, 131, 133, 139} two triple screening,^{116, 139} one triennial and quadrennial screening¹³³ and a final one additionally evaluated screening rounds every 5, 10, or 20 years.¹³⁰ Multiple studies varied the screening interval in scenario analyses, of which the impact will be discussed further in Section 4.3.2.

Patient identification & enrolment, summarized in column 5 of Table 18, are important factors in a screening programme as they largely determine the participation and adherence rate of eligible individuals. Additionally, the initiatives taken to identify and contact potentially eligible individuals are important cost drivers of any screening programme. Remarkably, only less than half of the included studies (11 studies) reported the means or cost of patient identification and enrolment in the screening programme at least to some degree.^{116, 118, 124, 125, 127-129, 131, 139-141} The means for reaching the potentially eligible individuals vary greatly between studies. Gomez-Carballo et al.¹²⁵ identified eligible screening candidates by sending a letter and leaflet and calling all Spanish individuals aged between 50-75 years old, which corresponded to 14 538 677 Spanish citizens, and included this cost in the analyses. Yuan et al.^{128, 129} as well as Zhao et al.¹³¹ took into account a cost for publicity and participant management without explicitly discussing how the screening programme was organized and participants were reached. Three studies based initial identification on physician recruitment and GP records.^{116, 118, 139} In two of those studies, this initial identification was followed by other means to identify the truly eligible population. Griffin et al.¹³⁹ used a self-assessment questionnaire as this study used a risk



prediction tool to identify the population eligible for screening. Of note, while Griffin et al.¹³⁹ included a cost related to the administration, scoring, and follow-up related to the questionnaires, they did not take into account a cost of screening GP records. The authors argued this cost would be marginal. The HTA performed by UK NSC took more steps to identify and enroll eligible screening candidates and is the most detailed in its approach. After screening the GP records for patients who are between 55-80 years old and ever-smokers (current or former smokers), those identified receive an invitation to call for a telephone lung cancer risk assessment to evaluate their eligibility based on the risk assessment tool LLPv2. Up to two reminder letters were sent to make this call. Those with a risk above the pre-specified risk threshold were invited to a LDCT scan and received an appointment letter. The full cost of this approach was taken into account in the analyses.¹¹⁶ Cressman et al.¹²⁴ used a variety of channels to reach potential eligible candidates by following the design of the ILST: radio, television, newspaper, paid social media ads, mail-out invitations, general practice clinics. While they did take into account a cost for the risk assessment, they seem not to have included a cost for screening advertisements using the previously mentioned channels. Finally, two studies assumed a cost for identifying the eligible population based on the colorectal cancer screening programme but did not describe the means of patient identification.^{140, 141}

Finally, a selection of studies included a **smoking cessation programme** as integral part of their screening intervention. Column 6 of Table 18 shows that four studies evaluated a lung cancer screening programme combined with a smoking cessation intervention.^{129, 132, 133, 138} Diaz et al.¹³³ evaluated two possible smoking cessation interventions (i.e., brief or intensive intervention) in combination with various screening intervals in the base case analyses. The brief intervention strategy was based on the 5 A's method developed by the Agency for Health Care Policy and Research in the United States. In it, healthcare providers ask every patient about their

tobacco use, advise smokers to quit, assess smokers' willingness to make a quit attempt, assist smokers in their quit attempt and arrange follow-up contacts. The intensive intervention for quitting smoking is a behavioural and drug-based treatment over a 12-month period. Smoking cessation interventions were evaluated assuming different frequencies (once, twice, and thrice in a lifetime) and starting age (35, 40 and/or 45 years). Yuan et al.¹²⁹ evaluated a nurse-led smoking cessation intervention consisting of counselling and pharmacotherapy which were offered the first time a participant was screened. In contrast, Cadham et al.¹³² evaluated five different smoking cessations as part of a lung cancer screening programme. These include pharmacotherapy alone and four variations of counselling combined with pharmacotherapy (i.e., web-based, telephone, group, and individual counselling), which were also offered at the individual's first screening only. Finally, in Evans et al.¹³⁸ the smoking cessation intervention included nicotine replacement therapy (nicotine replacement therapy patch + short-acting products), varenicline and 15-minute weekly counselling sessions for 12 weeks. In contrast to the previously discussed studies this smoking cessation intervention could be offered to a participant up to ten times if the individual was still smoking. In addition to these four studies, Behar Harpaz et al.¹²² mentioned taking into account the additional effects of a hypothetical smoking cessation programme in the sensitivity analyses by altering the smoking cessation rates but did not account for the additional costs this programme would induce. Seven studies explicitly mentioned not combining a smoking cessation programme with lung cancer screening, whilst the remaining seven studies did not disclose whether they included a smoking cessation programme or not.


Table 18 – Population, Intervention, Comparator, and Outcome(s) considered in academic publications (2020-2023) & HTAs

	Population eligibility criteria			Intervention		Comparator	Outcome
	Age criteria	Smoking history	Screening interval(s)	Identification & enrolment	Smoking cessation intervention		
Academic publications							
Behar Harpaz, 2023 ¹²²	<u>NLST</u> : 55-74 <u>NELSON</u> : 50-74	<u>NLST</u> : 30+ PY; Currently smoking or <15y since quitting <u>NELSON</u> : currently smoking or <10y since quitting with either >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years	<u>NLST</u> : 0, 1, 2 <u>NELSON</u> : 0, 1, 3, 5	Not reported	In SA, but no cost of SC programme	No screening	ICER (AU\$/LYG) ICER (AU\$/QALY gained)
Al Khayat, 2022 ¹²³	Start ages: 50, 60, 70 Stop ages: 60, 70, life-time	<u>NELSON</u> : ≥30y with ≥15 cigarettes/day and <10y since quitting Current or former smokers	Annual	Not reported	Not reported	No screening	ICER (€/QALY gained)
Cressman, 2022 ¹²⁴	PLCO _{m2012} 1.51%/6y vs. 55-80 (USPSTF-2013)	PLCO _{m2012} : 1.70%/6y vs. 30+ PY Currently smoking or <15y since quitting Current or former smokers (USPSTF-2013)	<u>ILST</u> : 0, 2	<u>ILST</u> : radio, television, newspaper, paid social media ads, mail-out invitations, general practice clinics Not clear whether advertisement cost is included Risk assessment cost included	Advice to stop included in ILST protocol, but no SC programme	USPSTF-2013 eligibility criteria	ICER (US\$/QALY gained)
Gomez-Carballo, 2022 ¹²⁵	<u>NELSON</u> : 50-74	<u>NELSON</u> : currently smoking or <10y since quitting with either >15 cigarettes/day for >25 years or >10	Years 0, 1, 3	Letter, leaflet and call Cost included	Not reported	No screening	ICER (€/LYG) ICER (€/QALY gained)



	Population eligibility criteria			Intervention		Comparator	Outcome
	Age criteria	Smoking history	Screening interval(s)	Identification & enrolment	Smoking cessation intervention		
		cigarettes/day for >30 years					
Kim, 2022 ¹²⁶	Base case: 55-74 Scenarios: 55-99	30+ PY Current or former smokers	Annual Biennial in scenario analysis	Not reported	Not included	No screening	ICER (US\$/QALY gained)
Nagy, 2022 ¹²⁷	Base case: 55-74 Scenarios start age: 50, 55	25+ PY Current smokers Scenario for general population	<u>Scenarios:</u> annual, biennial	Not clear Cost of two registered letters and envelopes included	Not reported	No screening	ICER (€/QALY gained)
Yuan, 2022a ¹²⁸	Base case: 50-74 Scenarios start age: 40, 45, 50, 55, 60, 65, 70	30+ PY Currently smoking or <15y since quitting. Current or former smokers	Annual	Screening publicity and management costs included	Not included	No screening	ICER (US\$/QALY gained)
Yuan, 2022b ¹²⁹	Scenarios start age: 45, 50, 55, 60, 65, 70 Stop age: 74	Scenarios smoking history: 20+, 25+, 30+ PY Currently smoking or <15y since quitting Current or former smokers	Annual	Screening publicity and management costs included	Nurse-led individual counselling + pharmacotherapy	No screening and screening without smoking cessation intervention	ICER (US\$/QALY gained)
Zeng, 2022 ¹³⁰	30-79 (scenarios for start age)	Smoking history not defined Number of eligible participants based on LC prevalence data	<u>Scenarios:</u> One-off, annual, biennial, 5 years, 10 years, 20 years	Not reported	Not reported	No screening	ICER (US\$/QALY gained)
Zhao, 2022 ¹³¹	Scenarios start age: 50, 55, 60, 65, 70 Stop age: 79	20+PY Current smokers	<u>Scenarios:</u> one-off, annual	Cost of public advertising and invitation management included	Not included	No screening	ICER (CNY/QALY gained)



	Population eligibility criteria			Intervention		Comparator	Outcome
	Age criteria	Smoking history	Screening interval(s)	Identification & enrolment	Smoking cessation intervention		
Cadham, 2021 ¹³²	55-80	30+ PY Currently smoking or <15y since quitting Current or former smokers	Annual	Not reported	5 smoking cessation interventions	Screening without smoking cessation interventions	ICER (US\$/QALY gained)
Diaz, 2021 ¹³³	Base case: men aged 55-65 Stop age varies in function of screening intervals	30+ PY Current or former male smokers	<u>Scenarios:</u> One-off, annual, biennial, triennial, quadrennial	Not reported	Brief intervention (5 A's*) Intensive intervention (behavioural & medication)	No screening Screening without smoking cessation interventions Smoking cessation intervention alone	ICER (€/QALY gained)
Esmaeili, 2021 ¹³⁴	55-74	13-38 PY	Triennial	Not reported	Not reported	No screening	ICER (IRR/QALY gained)
Sun, 2021 ¹³⁵	Scenarios for start age: 40, 45, 50, 55, 60 Stop age: 76	20+ PY Current smokers	Annual	Not clear	Not included	No screening	ICER (US\$/QALY gained)
Toumazis, 2021 ¹³⁶	50-80 (USPSTF-2021) vs. 55-80 (USPSTF-2013)	20+PY Currently smoking or <15y since quitting (USPSTF-2021) vs. 30+PY Currently smoking or <15y since quitting (USPSTF-2013) Scenarios time since quitting (20, 25)	Annual	Not reported	Not included	USPSTF-2013	ICER (US\$/QALY gained)
Du, 2020 ¹³⁷	50-75 Scenarios start age: 50, 55, 60 Scenarios stop age: 75, 80, 85	≥20 cig/day Current smokers	<u>Scenarios:</u> annual, biennial	Not reported	Not reported	No screening	ICER (€/LYG)



	Population eligibility criteria			Intervention		Comparator	Outcome
	Age criteria	Smoking history	Screening interval(s)	Identification & enrolment	Smoking cessation intervention		
Evans, 2020 ¹³⁸	55-74	30+ PY Currently smoking or <15y since quitting Current or former smokers	Annual	Not reported	Nicotine replacement therapy + varenicline + 15min counselling/w for 12w	Screening without smoking cessation intervention	ICER (CA\$/QALY gained)
Griffin, 2020 ¹³⁹	55-80 Scenarios for start and stop age within age window.	<u>Risk threshold</u> : 3%, 4% or 5% with LLPv2 Current or former smokers	<u>Scenarios</u> : One-off, triple screen, biennial, annual	GP records & questionnaire Only costs related to the questionnaire included	Not included	No screening	ICER (£/QALY gained)
Jaine, 2020 ¹⁴⁰	Base case: 55-74 Scenarios: 55-59; 60-64; 65-69; 70-74	30+ PY Currently smoking or <15y since quitting Current or former smokers Scenario for current smokers only	Biennial for 20 years	Based on colorectal screening Cost included	Not included	No screening	ICER (NZ\$/QALY gained)
McLeod, 2020 ¹⁴¹	Base case: 55-74 Scenarios: 55-59; 60-64; 65-69; 70-74	30+ PY Currently smoking or <15y since quitting Current or former smokers	Biennial	Based on colorectal screening Cost included	Not reported	No screening	ICER (NZ\$/HALY gained)
Veronesi, 2020 ¹⁴²	55-79	30+ PY Currently smoking or <15y since quitting Current or former smokers	Annual for 5y	Not included	Not included	No screening	ICER (€/LYG) ICER (€/QALY gained)
Health technology assessments (HTAs)							
UK NSC, 2022b ¹¹⁶	Base case: 55-80 Scenarios for start age (55 or 60) and stop age (75 or 80)	<u>Risk threshold</u> : 3%, 4% or 5% with LLPv2 Current or former smokers	<u>Scenarios</u> : One-off, triple screen, biennial, annual	Primary care data, notice, letter, reminder, telephone, invitation letter Costs included	Not included	No screening	ICER (£/QALY gained)



	Population eligibility criteria			Intervention		Comparator	Outcome
	Age criteria	Smoking history	Screening interval(s)	Identification & enrolment	Smoking cessation intervention		
IHE, 2014 ¹¹⁸	55-75	30+ PY Current or former smokers	<u>Scenarios:</u> biennial, annual	Physician recruitment Cost included	Not reported	No screening	ICER (CA\$/QALY gained)

*Notes: *5 A's = Ask every patient about their tobacco use, Advise smokers to quit, Assess smokers' willingness to make a quit attempt, Assist smokers in their quit attempt and Arrange follow-up contacts. Abbreviations: NLST = National Lung Screening Trial, NELSON = Nederlands-Leuven Longkanker ScreeningsONderzoek, PY = Pack Years, ILST = International Lung Screening Trial, LLPv2 = Liverpool Lung Project model – version 2, PLCOM12 = Prostate Lung Cancer Colorectal and Ovarian Cancer Screening Measure, ICER = Incremental Cost-Effectiveness Ratio, SA = Sensitivity Analysis, SC = Smoking Cessation, HALY = Health-Adjusted Life Year, USPSTF = United States Preventive Services Task Force, QALY = Quality-Adjusted Life Year, LYG = Life Year Gained.*

4.2.2.3. Comparator

The **comparators** used in each study are summarized in column 7 of Table 18. As formulated in the inclusion & exclusion criteria (Table 14), this report only included studies reflecting the standard of care situation in Belgium, which corresponds to the absence of a screening programme for lung cancer, studies comparing lung screening strategies, or studies examining the added value of a smoking cessation intervention within a screening programme. 19 of the 23 included studies compared lung cancer screening to a no-screening alternative. While Cressman et al.¹²⁴ compared the use of a risk assessment tool to the use of the USPSTF-2013 eligibility criteria, Toumazis et al.¹³⁶ evaluated the cost-effectiveness of the USPSTF-2021 eligibility criteria compared to the USPSTF-2013 eligibility criteria in the base case analyses. Most of the studies assessing the integration of a smoking cessation intervention into the screening intervention use a screening programme without a smoking cessation intervention as comparator. An exception is Diaz et al.¹³³, who compared the screening programme combined with a smoking cessation intervention to a situation without screening and without smoking cessation intervention as well as to a situation without lung cancer screening but with smoking cessation intervention. In addition, the analyses of Diaz et al. allow for a comparison to be made between a situation with lung cancer screening but without smoking cessation intervention and a situation without screening and

without smoking cessation intervention. Interestingly, Yuan et al.¹²⁹ combined the former two approaches by using two comparators: a screening programme without smoking cessation interventions and a situation without lung cancer screening.

4.2.2.4. Outcome

As shown in column 8 of Table 18, all studies used the Incremental Cost-Effectiveness Ratio (ICER) as **primary outcome**. A total of 22 studies expressed the ICER as incremental cost/QALY gained. In contrast, the study of Du et al.¹³⁷ did not take into account the quality of life in the analyses and only expressed the ICER as incremental cost/LYG. Three studies reported the incremental health of the screening programme both in terms of LYG and QALYs gained.^{122, 125, 142}



Key points

Population

- In general, two methodologies were applied by the included studies to define the screen-eligible population:
 1. Combination of age and smoking history (19/23 studies);
 2. Risk assessment tools.
- In most studies (7/23), in the base case, participants aged 55-74 with a smoking history of at least 30 pack-years who are either currently smoking or have quit in the past 15 years are eligible for screening. These criteria are in line with the NLST.
- In the more recent studies (3/23), the age criterium in the base case is often broadened to 50-74/5 to fit the NELSON age eligibility criteria. In addition, Behar-Harpaz et al.¹²² compared both the NLST and NELSON eligibility criteria (including the age criteria) to a situation without screening.
- There is considerable variation in the smoking history criterium across the studies. The majority of studies (12/23) uses a combination of pack years and time since quitting smoking to define the smoking history eligibility criterium. A minority of studies (4/23) only includes current smokers in the base case and a selection of studies (4/23) targeting both current and former smokers only take the PY into account without defining a time since quitting. Three studies opted for a pre-defined risk threshold resulting from an individual risk assessment tool from either the LLPv2 or PLCO_{M12}.
- The proposed risk assessment tools generally take more variables into account (including education, sex, COPD, BMI, etc.) in predicting the risk for lung cancer, but require more data on the population.
- Some studies focused on sub-populations (e.g., only men, only current smokers) of the full population.

Intervention

- Substantial variations in screening intervals could be observed in the included studies. Annual screening was most often evaluated in the base case (9/23) and the sensitivity analyses (8/23).
- The screening interval used in the NLST (0y-1y-2y) was only used by Behar-Harpaz et al.¹²², who compared the cost-effectiveness of the screening protocols of NLST and NELSON (0y-1y-3y-5y). In addition, Gomez-Carballo et al.¹²⁵ also examines the NELSON strategy but leaves out the final screening round (0y-1y-3y).
- Alternative screening intervals include biennial screening, triennial screening, and a single screen.
- In less than half of the studies multiple screening intervals were evaluated with the aim of identifying the most cost-effective screening interval. Of note is the study of Behar Harpaz et al.¹²², which compares the cost-effectiveness of the NLST and NELSON eligibility criteria respectively.
- Remarkably, only a minority of studies disclosed the means of patient identification & enrolment. Even less studies incorporated a cost for this aspect in their analyses.
- The vast majority of studies did not include an integrated smoking cessation programme in the evaluated lung cancer screening programmes. Four studies explicitly examined the added value of adding a smoking cessation intervention to screening in terms of cost-effectiveness.

Comparator

- With the exception of four studies, all included studies compared lung cancer screening without smoking cessation intervention to a no-screening alternative without smoking cessation intervention.



- Other studies either compared the cost-effectiveness of screening eligibility criteria (e.g., Cressman et al.¹²⁴ and Toumazis et al.¹³⁶) or examined the cost-effectiveness of adding a smoking cessation programme to a screening programme without a no-screening alternative (e.g., Cadham et al.¹³² and Evans et al.¹³⁸).

Outcome

- All but one study expressed the ICER as incremental cost/QALY gained by incorporating QoL in the analyses.
- Only three studies reported both LYG and QALYs gained to express the incremental health gains.

4.2.3. Model inputs: effectiveness of lung cancer screening and quality of life

This section describes the sources and methods used to embed the clinical effectiveness and quality of life in the health economic models. Table 19 summarizes the methods and sources used to incorporate the clinical effectiveness and quality of life in the models.

The primary sources of lung cancer screening **effectiveness**, mostly expressed as a stage shift from later stages of lung cancer to earlier stages, are shown in column 2 of Table 19. All included studies used trial-based data to model the clinical effectiveness of the respective examined lung cancer screening programmes. Interestingly, six of the included studies still relied exclusively on the NLST data for modelling the clinical effectiveness.^{116, 118, 132, 139, 140} This is remarkable as the results of the NLST date back to 2011 and since then, other large clinical trials have been published (e.g., NELSON). An additional six studies used a combination of NLST data and data gathered from one or more other trials (COSMOS, PLCO trial, canSPUC, NELSON, UK LCST, etc.).^{122, 128, 129, 133, 136, 142} With the publication of the NELSON study results in 2020, four studies solely relied on NELSON data for estimating the effectiveness of the proposed lung

cancer screening programmes.^{123, 125, 137, 141} In addition, three studies used NELSON data in combination with data from other trials (i.e., canSPUC, NLST).¹²⁷⁻¹²⁹ Noteworthy is the study of Behar Harpaz et al.,¹²² which developed two separate models for assessing the cost-utility of a lung cancer screening programme based on either the NLST or NELSON data, respectively. The remaining studies each used different sources for modelling the clinical effectiveness, including but not limited to the ILST, K-LUCAS, MILD, PanCan, canSPUC + ruraSPUC, etc.^{124, 126, 130, 131, 133, 135, 138} The critical appraisal of the clinical effectiveness found in each of the abovementioned randomized controlled trials is of prime importance when evaluating the cost-effectiveness of a lung cancer screening programme. For more information on the design, methods, results, strengths, and limitations of the relevant clinical trials, we refer to Chapter 1.1.1.1 of this report.

The majority of studies defines the stages of lung cancer from stage I to stage IV (with or without subdivisions) in their models, followed by the classification “localized-regional-distant”. Utility values were mostly literature-based, but originate from a large variety of underlying studies and vary considerably between these studies. More than half of the selected studies performing cost-utility analysis (13/22) did not report the QoL instrument. EQ-5D was the predominantly reported QoL instrument. Behar Harpaz et al.¹²² and Cressman et al.¹²⁴ opted for the SF-6D and Al Khayat et al.¹²³ for the more extensive SF-36. Despite the wide selection of underlying QoL studies, the most frequently cited reference for the health utilities is Tramontano et al.¹⁹⁶ UK NSC¹¹⁶ performed a systematic review to identify and assign utility values to the different lung cancer stages in their model. While more recent sources were identified, the authors opted for the utilities reported by Tramontano et al.¹⁹⁶ in the base case analysis. Only a handful of studies used disutilities to correct for screening-specific factors, of which the majority was assumption-based (e.g., indeterminate findings, false positives, etc.; see section 3.2.5 for the screening-specific factors).^{116, 122, 127, 139} Six studies used age-specific^{122, 126, 127, 132, 136, 138} and three studies^{127, 132, 138} gender-specific utility values in their models.



Table 19 – Effectiveness and Quality of Life measures used in academic publications (2020-2023) & HTAs

Study	Primary source of clinical effectiveness	Stages and associated utilities	QoL source(s)/ instrument	Disutilities
Behar Harpaz, 2023 ¹²²	NLST NELSON	I: 0.71 II: 0.68 III: 0.67 IV: 0.66 Unknown: 0.68	<u>Baseline utilities:</u> 45 and Up Study ^{197, 198} <u>Cancer stage utilities:</u> Cancer Care Outcomes Research and Surveillance Study ¹⁹⁶ SF-6D derived from SF-12	<u>Age:</u> ¹⁹⁹ +70: -0.01 +80: -0.04 <u>Screening result:</u> -0.02 for 2 weeks <u>Follow-up CT:</u> -0.02 for 3 months <u>False positives:</u> -0.71 for 3 months
Al Khayat, 2022 ¹²³	NELSON	I: 0.72 II: 0.67 III: 0.645 IV: 0.62 Follow-up: 0.80	<u>Literature-based:</u> Black et al. ¹⁷² SF-36	None reported
Cressman, 2022 ¹²⁴	ILST	Screen (no LC) ¹⁷² : 0.85 No screen (no LC) ¹⁹⁹ : 0.87 Curative treatment ¹⁹⁶ : 0.82 Non-curative treatment y1 ¹⁹⁶ : 0.78 Non-curative treatment y2-19 ¹⁹⁶ : 0.50 Progression after curative treatment y1 ²⁰⁰ : 0.69 Progression after curative treatment y2-19 ²⁰⁰ : 0.75	<u>Literature-based:</u> Cressman et al. ²⁰¹ Ngo et al. ¹⁹⁹ Tramontano et al. ¹⁹⁶ Jang et al. ²⁰⁰ SF-6D and EQ-5D-3L	None reported
Gomez-Carballo, 2022 ¹²⁵	NELSON	All states: 0.891 Surgery: 0.825 Surgery+chemotherapy: 0.70 Surgery+chemotherapy+radio: 0.70 Chemotherapy+radio: 0.573 Immunotherapy ²⁰² : 0.70 Aftercare I: 0.825 Aftercare II: 0.825 Aftercare III: 0.772 Aftercare IV: 0.573 Palliative care ²⁰³ : 0.33	<u>Literature-based:</u> Hofer et al. ¹⁵⁶ (EQ-5D) Paracha et al. ²⁰² Nafees et al. ²⁰³ EQ-5D	None reported
Kim, 2022 ¹²⁶	K-LUCAS trial	Localized: 0.660 Regional: 0.463 Distant: 0.310	<u>Utility weights of smokers:</u> Korean National Health and Nutrition Examination Survey (KNHANES) <u>Health states:</u> Korean utility study for lung cancer-related health states ²⁰⁴ Instrument not reported	<u>Age:</u> 55-59y: 0.942 60-64y: 0.944 65-69y: 0.916 70-74y: 0.880 75-79y: 0.887 ≥ 80y: 0.829



Study	Primary source of clinical effectiveness	Stages and associated utilities	QoL source(s)/ instrument	Disutilities
Nagy, 2022 ¹²⁷	NELSON HUNCHEST	Screening: 0.823 Indeterminate result – follow-up: 0.793 Examination tunnel: 0.820 No LC: 0.823 Non-diagnosed LC: 0.823 Resection only: 0.701 Resection + adjuvant therapy: 0.721 Neoadjuvant therapy ²⁰⁵ : 0.741 No resection ²⁰⁵ : 0.534 Supportive care ¹⁸⁵ : 0.655 After operation, no LC: 0.691 After operation, progressed LC: 0.541 After operation, non-diagnosed LC: 0.691	<u>Literature-based:</u> Grutters et al. ²⁰⁶ Manser et al. ¹⁸⁵ Trippoli et al. ²⁰⁵ Adapted to Hungarian EQ-5D	<u>Indeterminate result:</u> -0.0345 for 3 months Adjusted to age- and sex-specific utility tariffs
Yuan, 2022a ¹²⁸	canSPUC, NLST, NELSON	I: 0.85 II: 0.75 III: 0.69 IV: 0.69	<u>Literature-based:</u> Zhu et al. ²⁰⁷ Blom et al. ²⁰⁸ Zeng et al. ²⁰⁹ Instrument not reported	None reported
Yuan, 2022b ¹²⁹	canSPUC, NLST, NELSON	I: 0.85 II: 0.75 III: 0.69 IV: 0.69	<u>Literature-based:</u> Zhu et al. ²⁰⁷ Blom et al. ²⁰⁸ Zeng et al. ²⁰⁹ Instrument not reported	None reported
Zeng, 2022 ¹³⁰	canSPUC ruraCSP	Localized: 0.823 Regional: 0.772 Distant: 0.573	<u>Literature-based:</u> Sturza et al. ²¹⁰ Instrument not reported	None reported
Zhao, 2022 ¹³¹	Wenling lung cancer screening programme	Carcinoma In Situ ²¹¹ : 0.87 I: 0.84 II: 0.84 III: 0.87 IV: 0.75	<u>Literature-based:</u> Chen ²¹¹ Field et al. ⁶⁰ Instrument not reported	None reported
Cadham, 2021 ¹³²	NLST	I: 0.71 II: 0.68 III: 0.67 IV: 0.66 Limited SCLC: 0.69 Extensive SCLC: 0.66 Terminal SCLC: 0.62	<u>Literature-based:</u> Criss et al. ¹⁵³ Hanmer et al. ²¹² Tramontano et al. ¹⁹⁶ van den Hout et al. ²¹³ Instrument not reported	Utilities applied to age- and sex-specific general health utilities to determine QALYs



Study	Primary source of clinical effectiveness	Stages and associated utilities	QoL source(s)/ instrument	Disutilities
Diaz, 2021 ¹³³	NLST UK Lung Cancer Screening Trial UK Lung Cancer RCT Pilot Screening Trial	I-II: 0.705 IIIa: 0.655 IIIb-IV: 0.530	<u>Literature-based:</u> Sturza et al. ²¹⁰ Trippoli et al. ²⁰⁵ Instrument not reported	None reported
Esmaeili, 2021 ¹³⁴	Pilot Pomeranian lung cancer screening program	Curative NSCLC: 0.88 Non-curative NSCLC: 0.78	<u>Literature-based:</u> Tramontano et al. ¹⁹⁶ EQ-5D-5L	None reported
Sun, 2021 ¹³⁵	canSPUC (stage distribution usual care) NLCSIP (stage distribution LCS)	Early-stage LC: 0.825 Non-early-stage LC: 0.573	<u>Literature-based:</u> Sturza et al. ²¹⁰ Instrument not reported	None reported
Toumazis, 2021 ¹³⁶	NLST & prostate, lung, colorectal, ovarian cancer screening study	I: 0.71 II: 0.68 III: 0.67 IV: 0.66 Limited SCLC: 0.69 Extensive SCLC: 0.66 Terminal phase: 0.62	<u>Survey data:</u> LC patients diagnosed in 2003-2005 <u>Literature-based:</u> Tramontano et al. ¹⁹⁶ McMahon et al. ¹⁷⁹ EQ-5D-5L	<u>Age</u> ²¹² : 40-49y: 0.868 50-59y: 0.838 60-69y: 0.824 70-79y: 0.786 ≥ 80y: 0.747
Du, 2020 ¹³⁷	NELSON	No utilities taken into account (CEA)	/	/
Evans, 2020 ¹³⁸	OncoSim – Lung (NLST)	<u>Stage I-III:</u> Diagnosis: 0.809 Surgery & immediate follow-up: 0.592 Radiotherapy for medically inoperable: 0.632 Adjuvant chemotherapy: 0.601 Concurrent chemotherapy & radiotherapy: 0.469 Surveillance after treatment: 0.828 <u>Stage IV:</u> Diagnosis: 0.439 Chemotherapy: 0.326 Prophylactic cranial irradiation: 0.343 Palliative radiotherapy: 0.222 Supportive care only: 0.484 End of life care: 0.179	<u>Literature-based:</u> Boswell et al. ²¹⁴ Instrument not reported	<u>Female</u> ²¹⁵ : 50-54y: 0.842 55-59y: 0.830 60-64y: 0.841 65-69y: 0.837 70-74y: 0.831 75-79y: 0.778 80-84y: 0.736 <u>Male</u> ²¹⁵ : 50-54y: 0.856 55-59y: 0.850 60-64y: 0.842 65-69y: 0.848 70-74y: 0.841 75-79y: 0.809 80-84y: 0.748
Griffin, 2020 ¹³⁹	NLST	Baseline utility of female smokers ⁰⁶ : 0.753 Baseline utility of male smokers ⁰⁶ : 0.782 I: baseline utility II: 0.77 III: 0.77 IV: 0.76	<u>Literature-based:</u> Craig et al. ²¹⁶ Tramontano et al. ¹⁹⁶ EQ-5D-5L	<u>Screening:</u> -0.01 for 2 weeks <u>False positive:</u> -0.063 for 3 months



Study	Primary source of clinical effectiveness	Stages and associated utilities	QoL source(s)/ instrument	Disutilities
Jaine, 2020 ¹⁴⁰	NLST	Not reported	Global Burden of Disease 2010 study and New Zealand specific estimates (source unknown) Instrument not reported	<u>Disability weights:</u> ^{217, 218} LC diagnosis & treatment first 5 months: -0.469 Terminal 1 month: -0.548 Preterminal LC 5 months: -0.539 After diagnosis yearly: -0.315 Complication from diagnostic test: -0.0158
McLeod, 2020 ¹⁴¹	NELSON	Not reported	Global Burden of Disease 2010 study and New Zealand specific estimates (source unknown) Instrument not reported	<u>Disability weights:</u> ^{217, 218} LC diagnosis & treatment first 5 months: -0.469 Terminal 1 month: -0.548 Preterminal LC 5 months: -0.539 After diagnosis yearly: -0.315 Complication from diagnostic test: -0.0158
Veronesi, 2020 ¹⁴²	NLST (stage distribution usual care) COSMOS (stage distribution LCS)	Not reported	Unclear	None reported
UK NSC, 2022b ¹¹⁶	NLST	IA & IB: 0.81 IIA & IIB: 0.77 IIIA & IIIB: 0.77 IV: 0.76	<u>Literature-based:</u> Tramontano et al. ¹⁹⁶ EQ-5D-5L	<u>In scenario analyses:</u> Screening: -0.01 for 2 weeks ⁶⁸ False positive: -0.063 for 3 months ²¹⁹
IHE, 2014 ¹¹⁸	NLST	Not reported	Population Health Impact of Disease in Canada study Instrument not reported	None reported

Abbreviations: NLST = National Lung Screening Trial, NELSON = Nederlands-Leuven Longkanker ScreeningsOnderzoek, ILST = International Lung Screening Trial, canSPUC = Cancer Screening Program in Urban China, COSMOS = Continuous Observation of Smoking Subjects, LC = lung cancer, SC = small cell, NSC = non-small cell, LCS = Lung Cancer Screening, QALY = Quality-Adjusted Life Year, CEA = Cost-Effectiveness Analysis.



Key points

Clinical effectiveness

- All included studies based the clinical effectiveness of lung cancer screening on trial-based data.
- Many studies used either the NLST or NELSON clinical effectiveness in their models. However, most authors supplement the data of these large trials with smaller, often local clinical trials.
- Despite the availability of more recent clinical trial data, the NLST was still most often used as the primary source for clinical effectiveness.

Stages & QoL

- The majority of studies classifies the stages of lung cancer from stage I to stage IV (with or without subdivisions).
- The most frequently used alternative classification in the included studies is “Localized – Regional – Distant”.
- Utility values were mostly literature-based, but originate from a large number of studies. The most frequently cited reference for the health utilities is Tramontano et al.¹⁹⁶

Disutilities

- Only a handful of studies used disutilities to correct for screening-specific circumstances (e.g., indeterminate findings, false positives, etc.; see section 4.2.5 for the screening-specific factors).

4.2.4. Model inputs: costing

Most studies relied on multiple sources for assigning costs within their models, including government (agencies') data, (pilot) studies, previous publications, and/or hospital data. There is considerable variability in the sources used to retrieve costs which may be attributed to the substantial variety of countries in which the studies were performed as costs are considered to be highly country-specific. Appendix 6 Table 114 summarizes the various costs which were considered in the included studies. In general, the costs taken into account by the included studies can be subdivided into three categories: (1) screening-specific costs, (2) cost of lung cancer diagnosis, and (3) cost of lung cancer treatment.

The lung cancer screening-specific costs are defined as all costs arising from the lung cancer screening programme. This cost includes both the costs of organizing the screening programme itself (e.g., invitation of screen-eligible participants, LDCT scans, etc.) as well as the costs associated with the potential harms of screening (e.g., false positives, overdiagnosis, etc.). The principal cost of any lung cancer screening is being reported as the cost of the LDCT scans used to screen eligible candidates for lung cancer and was reported by 17 of the 23 studies. The cost of an LDCT scan in these studies varies between US\$50.42 (~€47) and NZ\$722.80 (~€407) with an average of €155 and a median of €175.⁹ Besides the cost of the LDCT scan, another principal cost of any screening programme is the cost of identifying and inviting the screening-eligible population for screening. As described previously, less than half of the included studies (11/23) described the means of identifying and inviting the screen-eligible population to some extent.^h Remarkably, while this cost may be substantial, even less studies (9/23) explicitly reported and included a cost for this crucial aspect of any screening programme.^{116, 118, 125, 127, 129, 131, 139-141} Cressman et al.¹²⁴ did report a cost for the risk assessment of the population, but did not explicitly report a cost for reaching this population. The remaining studies either reported a cost for screening without disclosing which cost elements were

⁹ See indicative currency exchange rates underneath Table 114.

^h For a discussion on the methods used to identify & invite the screening-eligible population, see Section 4.2.2.2.



included (5/23)^{124, 126, 130, 134, 135} or downsized the cost of the screening programme to solely an LDCT scan (8/23).^{122, 123, 128, 132, 133, 136, 137, 142} Evans et al.¹³⁸ mentioned they included the lung screening cost based on the OncoSim model, but they did not report which cost elements were taken into account as well as the monetary values of these costs. Besides the organization of the screening programme, additional costs induced by other factors related to screening (such as incidental findings, false positives, overdiagnosis, etc.) should be taken into account. However, only five studies reported costs taken into account for these factors. The reported costs were mainly related to the handling of false positives^{122, 139, 142} and incidental findings.^{140, 141} Due to the importance of the lung cancer screening-specific factors and the assigned costs, these elements are discussed more elaborately in Section 4.2.5 of this report (research question 2).

The majority of studies incorporated **costs for the diagnostic procedures** (17/23). In contrast, six studies did not report any cost for the diagnosis of lung cancer after a positive screening result.^{124, 126, 134, 135, 138, 142} Seven studies did not report which diagnostic procedures were taken into account by either reporting an overall cost for diagnosis or a cost for a diagnostic test without providing a more detailed description of this test.^{127-130, 137, 139-141} The most frequently reported diagnostic procedures were: needle biopsy, PET scan, bronchoscopy, VATS, miastinoscopy, and chest radiograph.

With regard to the **costs for lung cancer treatment**, more than half of the studies (15/23) stratified the treatment cost by cancer stage without detailing which procedures and cost elements were taken into account. This approach was used frequently as the (cost-)effectiveness of the screening programme was most often modelled as a stage shift from later stages to earlier stages of lung cancer. Four studies described the costs in substantially more detail by reporting the costs on a procedure-level (e.g., cost of chemotherapy).^{116, 118, 125, 127} The most frequently reported procedures in the treatment of lung cancer were: surgery, chemotherapy, radiotherapy, and immunotherapy. The four remaining studies did not disclose the lung cancer treatment costs used in their respective models.^{132, 133, 140, 141}

A selection of studies additionally took into account **costs outside of the three abovementioned categories**. Of note are the studies of Jaine et al.¹⁴⁰ and McLeod et al.¹⁴¹, which in addition to the abovementioned cost categories also assigned the average healthcare system cost of a civilian to both the individuals in the usual care and screening arms for each year they were alive to account for the additional healthcare costs of living longer due to screening. Furthermore, nine studies^{116, 118, 122, 123, 125, 127, 136, 138, 139} explicitly reported including the costs associated with palliative or end of life-care in their respective models, but different approaches were used and six of the studies did not disclose the monetary value of the assigned cost for palliative care.^{118, 123, 125} As described previously, five studies performed the analyses from a (limited) societal perspective. Kim et al.¹²⁶ stated taking a limited societal perspective by additionally including the costs of transportation, patient time, and caregiver time in comparison with the most frequently used healthcare system perspective. Zhao et al.¹³¹ added the costs of transportation and wages for missed work due to attending the screening. Both Cadham et al.¹³² and Sun et al.¹³⁵ claim performing the analyses from a societal perspective but did not disclose which societal costs were included, which makes it difficult to evaluate whether the societal perspective was truly applied. Diaz et al.¹³³ only included the direct medical costs related to lung cancer screening and consequently converted these costs to a societal perspective by taking a rather liberal assumption that societal costs are the fourfold of the direct medical costs. This means that the studies claiming to take a societal perspective suffer from substantial limitations by either not taking into account all societal costs or not transparently reporting which costs were considered. Finally, four studies evaluated the cost-effectiveness of integrating a smoking cessation intervention in a potential lung cancer screening programme. All four studies additionally took into account the costs of the proposed smoking cessation interventions on top of the previously described categories of relevant costs.^{129, 132, 133, 138}



Key points

The large majority of studies included costs subdivided in the following cost categories:

- Screening-specific costs (e.g., LDCT scan, identification & invitation, screening management, false positives, incidental findings)
- Cost of diagnosis (e.g., diagnostic test, PET scan, needle biopsy, bronchoscopy)
- Cost of lung cancer treatment (e.g., treatment cost per stage, chemotherapy, radiotherapy, immunotherapy, surgery)

Screening-specific costs

- Less than half of the studies (11/23) described the means of identifying and inviting the screen-eligible population. Even less (9/23) explicitly reported costs for identification & invitation of screen-eligible candidates.
- Five studies lack transparency on which cost components were included in the screening cost.
- The majority of studies fails to take into account sufficient relevant screening-specific costs (see section 4.2.5).
- The cost of an LDCT scan, identified as having a substantial impact on the ICER in section 4.3.2, varies between US\$50.42 (~€47) and NZ\$722.80 (~€407) with an average of €155 and a median of €175.

Cost of lung cancer treatment

- Most studies defined a cost for the treatment of each specific stage of lung cancer.
- Unfortunately, only a handful studies provided sufficient detail in the (cost of the) various procedures used in the treatment (e.g., chemotherapy, immunotherapy).

In general

- All studies included cost components from each of the three abovementioned cost categories, but many lack transparency.
- Most studies relied on multiple sources for assigning costs within their models, including government (agencies') data, (pilot) studies, previous publications, and/or hospital data.
- The studies claiming to have performed the analyses from the societal perspective did not include all societal costs and/or did not present the included costs transparently.

4.2.5. Factors of a lung cancer screening programme to be considered in economic evaluations

Based on previously published systematic reviews, health technology assessments, and primary economic evaluations, a specific set of factors could be identified which are important to consider in the health economic evaluation of a lung cancer screening programme. Table 20 summarizes the handling of these factors by each included study in their respective health economic models. The set of factors is composed of organizational variables (i.e., participation & adherence rate), potential harms of screening (i.e., specificity & false positives, sensitivity & false negatives, overdiagnosis), potential biases related to screening (i.e., lead-time bias, length bias), as well as the handling of indeterminate results and incidental findings.

The first two important factors to consider in the health economic evaluation of any screening programme is the **participation and adherence rate** of the screen-eligible population as a low participation and/or adherence rate would lead to substantial costs of identifying and inviting the entire screen-eligible population while only a fraction of this population (i.e., the screening participants) would experience the potential health benefits of the proposed screening programme with an unfavourable impact on the cost-effectiveness as a consequence. Overall, 15 of the 23 included studies clearly reported the assumed **participation rate** in their model. Five of these studies assumed a participation rate of 100%.^{131, 135-137, 142} This means that



a substantial amount of studies (13/23) either explicitly or implicitly assumed a rather unrealistic participation rate of 100% in their economic evaluations of lung cancer screening, which could lead to substantially biased cost-effectiveness estimates. Two of these studies stated basing their model inputs on the NLST and/or NELSON trials, but it is not clear whether the participation and/or adherence rate of these trials were taken over as well.^{122, 123} In the studies incorporating a non-100% participation rate, the assumed participation rate ranged between 15% and 84% with slightly more than half of the studies (6/10) opting for a participation rate above 50%. Only 5 of the 23 studies varied the participation rate in the sensitivity analyses, of which the impact will be discussed further in Section 4.3.2.^{116, 125, 132, 133, 137} The same overall trend is visible in the assumed **adherence rates** in the various models with only 11 studies reporting an adherence rate of which 6 assumed an adherence rate of 100%. The studies opting for a non-100% adherence rate assumed adherence rates between 35.32% and 95%.ⁱ Two studies varied the adherence rate in the sensitivity analyses.^{137, 138}

Both sensitivity and specificity, and the associated number of false negative and false positive cases, are additional factors with potentially large influences on the (cost)-effectiveness of screening programmes in general. The higher the **sensitivity** of the screening, the more likely it is that someone who actually has the disease will get a positive test result and the fewer false negative cases are missed by the screening protocol. A high number of false negative cases (i.e., low screening sensitivity) would not lead to additional costs on the short term as no diagnostic procedures and treatments will take place until the missed lung nodules will be picked up in a next screening round or when symptoms become visible. However, in the longer run, false negative cases will lead to later diagnosis and subsequently more sophisticated, radical, and subsequently more expensive procedures with an impact on both costs as well as survival and quality of life will be performed. The majority of the included studies (15/23) reported the

sensitivity of the proposed screening programme, which ranged from 60.4% to 99.9%.^{118, 127-135, 137, 139-142} Kim et al.¹²⁶ explicitly stated not taking into account the sensitivity and false negatives in their analyses, while four other studies based their inputs on the results of the NLST and/or NELSON trials without specifying the values used in their respective models and how the false negative cases were handled.^{116, 122, 125, 132} Du et al.¹³⁷ reported multiple sensitivity rates depending on the diameter of the lung nodule. There is considerable variation noticeable in the reported sensitivity over the various included studies with three studies reporting a sensitivity below 80%, four between 80% and 90%, and six above 90%. Only 6 of the 23 studies reported taking into account **false negatives** in their evaluations.^{123, 134, 135, 139, 140, 142} However, important to note is that studies which did not incorporate false negatives explicitly in their models, possibly do take false negatives into account implicitly as false negatives can be detected in an upcoming screening round or are included in the group of interval cancers. The handling of the false negatives in the models differed greatly. Veronesi et al.¹⁴² added a non-disclosed cost to false negative cases while Al Khayat et al.¹²³ assumed the false negative cases to be found in the next screening round. Esmaeili et al.¹³⁴ and Sun et al.¹³⁵ assumed the same clinical stage distribution as the non-screened population and likewise Jaine et al.¹⁴⁰ redistributed false negatives as lung cancer cases based on the baseline distribution of lung cancer. Finally, Griffin et al.¹³⁹ assumed a zero treatment and follow-up cost until the true diagnosis of lung cancer had been made. Unfortunately, in the remaining 9 of the 15 studies reporting the sensitivity of screening, the handling of false negative cases in the health economic model was not disclosed. To estimate the impact of sensitivity on the ICER, 10 of the 15 studies^{128-131, 133-135, 140-142} varied screening sensitivity (and subsequently the number of false negatives) in the sensitivity analyses with a third (3/10) finding sensitivity to have a substantial impact on the cost-effectiveness of a lung cancer screening programme.^{j133, 135, 142}

ⁱ Yuan et al.¹²⁸ refers to an adherence rate of 35.32%, but it is unclear whether this percentage was used as a participation rate or adherence rate in the analyses. Without the studies of Yuan et al. the adherence rate ranges between 70% and 95%.

^j A substantial impact was considered a 20% change or more in the ICER.



In addition to the sensitivity of the lung cancer screening programme, the **specificity** is often quoted as an important factor to consider when evaluating screening programmes. Specificity is defined as the percentage of true negative test results among non-sick persons. This means that lower rates of specificity are related to higher numbers of false positive cases. False positive results can impact the (cost-)effectiveness of lung cancer screening in several ways. First, the unnecessary diagnostic procedures following a false positive result lead to additional unnecessary costs as well as unnecessary adverse events and/or complications resulting from the diagnostic procedures. Second, multiple studies argue that a (false) positive screening result has a negative impact on the quality of life of participants due to increased anxiety levels. All but seven studies reported the specificity of the proposed lung cancer screening programme.^{124-126, 132, 133, 136, 138} Specificity in these publications amounted between 47% and 100%. As with the sensitivity of screening, there is considerable variation in the reported specificity values. Nagy et al.¹²⁷ reported a specificity below 50%, five studies between 60% and 80%, two studies between 80% and 90%, and eight studies above 90%. Unfortunately only six studies discussed how they handled the **false positives** resulting from screening.^{116, 122, 124, 134, 139, 142} Half of these studies^{124, 134, 142} solely assigned an additional cost to the false positive cases for the unnecessarily performed diagnostic procedures while the other half^{116, 122, 139} assigned both a cost and a temporary disutility to

false positive cases to additionally account for the increased anxiety levels due to a false positive screening result.^k UK NSC¹¹⁶ and Griffin et al.¹³⁹ opted for a disutility of 0.063 for three months while Behar Harpaz et al.¹²² assumed the same utility level as stage I lung cancer for 3 months. While Esmaeili et al.¹³⁴ did not specifically disclose the cost(s) assigned to false positive cases, the remaining studies used a fixed cost resulting from the work-up in case of false positive cases. Behar Harpaz et al.¹²² assumed a cost of AU\$861.6 (~€526) for false positives, while Veronesi et al.¹⁴² assumed a considerably higher cost for these cases of €2007. Griffin et al.¹³⁹ and UK NSC¹¹⁶ based the rate of consumption of diagnostic work-up on the UK Lung Screening (UKLS) trial and multiplied these by the unit costs resulting in a weighted mean cost of £435 (~€512).^l Cressman et al.¹²⁴ only reported the mean cost of false positives disaggregated by sex (females: \$83 (~€78), males: \$41 (~€39)), which seems considerably lower than the other studies. Unfortunately, 10 studies provided insufficient details on how false positive cases were handled in the health economic model. The majority of studies (13/16) did however vary either the specificity, the cost associated with a false positive, and/or the disutility associated with a false positive in the sensitivity analyses. Two studies found specificity and/or false positives to have a substantial impact on the cost-effectiveness of screening for lung cancer.^{140, 142}

^k UK NSC only applied the disutility in a scenario analysis, not in the base case.

^l UKLS consumption rates of post-LDCT diagnostic work-up in false positive cases: multidisciplinary team meeting (100%), follow-up CT (84.7%), out-

patient follow-up (30%), PET scan (18%), needle biopsy (9.7%), surgical referral (5.5%), EBUS (1.4%), oncology referral (1.4%).


Table 20 – Overview of factors considered in academic publications (2020-2023) & HTAs

Study	Participation	Adherence	Sensitivity	Specificity	False positives	False negatives	Lead-time bias	Length bias	Over-diagnosis	Indeterminate results	Incidental findings
Academic publications											
Behar Harpaz, 2023 ¹²²	Not reported (NLST & NELSON)	Not reported (NLST & NELSON)	Not reported	NLST: 91.8% NELSON: 98.8%	NLST: 8.2% NELSON: 1.2% Cost (AU\$861.1) taken into account Same utility as stage I LC	Not reported	Not reported	Not reported	NLST: 1.9%* NELSON: 5.3%*	Included Cost of follow-up CT Disutility of 0.02 over 3 months	Not included
Al Khayat, 2022 ¹²³	Not reported	Not included	Not reported	100%	Assumed 0	Assumed to be found in the next screening round	Not included	Not reported	Not included	Not reported	Not reported
Cressman, 2022 ¹²⁴	Not reported	Not reported	Not reported	Not reported	Rate not reported Cost taken into account** (no disutility)	Not reported	Not reported	Not reported	Not reported	Not reported	Costs: not clear Benefits: included
Gomez-Carballo, 2022 ¹²⁵	70%	Not reported	Not reported (NELSON)	Not reported (NELSON)	Not reported	Not reported	Not reported	Not reported	Not reported	Not clear	Not reported
Kim, 2022 ¹²⁶	Not reported	Not included	Not included	Not included	Not included	Not included	Not reported	Not reported	Not reported	Not reported	Not reported
Nagy, 2022 ¹²⁷	Smokers: 50.3%	Not reported	Baseline screen: 99.83%	Baseline screen: 48.98%	Baseline screen: 51.02%	Baseline screen: 0.17%	Not included	Not reported	Not included	Included	Not reported



Study	Participation	Adherence	Sensitivity	Specificity	False positives	False negatives	Lead-time bias	Length bias	Over-diagnosis	Indeterminate results	Incidental findings
	Gen. pop.: 60.2%		Annual /biennial screen: 99.90%	Annual /biennial screen: 47.33%	Annual/biennial screen: 52.67%	Annual/biennial screen: 0.10%				Disutility of 0.0345 over 3 months	
					Handling unclear	Handling unclear					
Yuan, 2022a ¹²⁸	Not reported	35.32%	93.7%	76.5%	23.5% Handling unclear	6.30% Handling unclear	Not reported	Not reported	11% (NLST)	Not reported	Not reported
Yuan, 2022b ¹²⁹	Not reported	35.32%	93.7%	76.5%	23.5% Handling unclear	6.30% Handling unclear	Not reported	Not reported	11% (NLST)	Not reported	Not reported
Zeng, 2022 ¹³⁰	Not reported	Not reported	87.7%	90.6%	9.4% Handling unclear	12.30% Handling unclear	Not reported	Not reported	Varied between 0% and 3%	Not reported	Not reported
Zhao, 2022 ¹³¹	100%	100%	79%	81%	19% Handling unclear	21% Handling unclear	Not reported	Not reported	Not reported	Not reported	Not reported
Cadham, 2021 ¹³²	Screening coverage: 15% (varied in SA) Smoking cessation programme: 100%	Not reported	Adapted from NLST	Not reported	Adapted from NLST Handling unclear	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Diaz, 2021 ¹³³	Coverage: 18.69% (varied in SA)	Not reported	60.4%	Not reported	Not reported	39.60% Handling unclear	Not included	Not reported	Not included	Not reported	Not included
Esmaili, 2021 ¹³⁴	Not reported	Not reported	87%	85%	15%	13%	Not reported	Not reported	10% (varied)	Not reported	Not reported



Study	Participation	Adherence	Sensitivity	Specificity	False positives	False negatives	Lead-time bias	Length bias	Over-diagnosis	Indeterminate results	Incidental findings
					Cost taken into account (cost of screening and pathology test)	Assumed same clinical stage distribution as unscreened individuals.			between 5% and 38%)		
Sun, 2021 ¹³⁵	100%	100%	87.70%	90.60%	9.40% Handling unclear	12.30% Same clinical stage distribution as non-screened	1y	Not reported	Varied between 0% and 20%	Not reported	Not included
Toumazis, 2021 ¹³⁶	100%	100%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Included (between 6% and 6.2%)	Not reported	Not reported
Du, 2020 ¹³⁷	100% (scenario with 50%)	100%	Diameter < 3 mm: 0% 3 mm ≤ diameter < 5 mm: (0.5*diameter-1.5)*100% Diameter ≥ 5 mm: 100%	99.2%	Men: 4.15%-7.64% Women: 4.09%-17.45% Handling unclear	Diameter < 3 mm: 100% 3 mm ≤ diameter < 5 mm: 1 - (0.5*diameter-1.5)*100% Diameter ≥ 5 mm: 0% Handling unclear	Not reported	Not reported	Not reported	Not reported	Not reported
Evans, 2020 ¹³⁸	40%	70% (varied in SA)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Griffin, 2020 ¹³⁹	46.5%	100%	70.9%	62.4%	37.60% Disutility of 0.063 for 3 months	29.10% Zero treatment and follow-up cost	Included	Included	31%	Included Cost of false positive	Not included



Study	Participation	Adherence	Sensitivity	Specificity	False positives	False negatives	Lead-time bias	Length bias	Over-diagnosis	Indeterminate results	Incidental findings
					and costs (£184.63) taken into account	until a true diagnosis of lung cancer				Disutility of false positive	
Jaine, 2020 ¹⁴⁰	Non-maori: 70% Maori: 64%	Not reported	93.8%	73.4%	26.60% Handling unclear	6.20% False negative screens in each year were redistributed as lung cancer cases in that year based on the NZ baseline stage distribution	0.5y	Not reported	Stage shift was modelled by removing the assumed level of overdiagnosis prior to the two-step stage shift process	Not reported	Cost of one imaging test and one consultation included
McLeod, 2020 ¹⁴¹	70%	Not reported	84.6%	98.6%	1.40% Handling unclear	15.4% Handling unclear	0.5y	Not reported	8.9%	Not reported	Not reported
Veronesi, 2020 ¹⁴²	100%	Y1: 100% Y2: 93% Y3: 88% Y4: 84% Y5: 79%	90.4%	99.3%	0.70% Cost (€2007) taken into account	9.60% Cost taken into account	2y	Not reported	0%	Included Cost of follow-up included Disutility: not included	Not reported
Health Technology Assessments (HTAs)											
UK NSC, 2022b ¹¹⁶	83.6% (scenarios)	100%	Not reported	96.3%	3.7% Disutility of 0.063 for 3 months and costs taken into account	Not reported	Included	Included	Included	Included Cost of follow-up included Disutility: not clear	Not included



Study	Participation	Adherence	Sensitivity	Specificity	False positives	False negatives	Lead-time bias	Length bias	Over-diagnosis	Indeterminate results	Incidental findings
IHE, 2014 ¹¹⁸	70% (scenarios 50-90%)	95%	90%	73%	27% Handling unclear	10% Handling unclear	Not reported	Not reported	Not reported	Not reported	Not included

Notes: * Overdiagnosis rates were calculated differently as the model used in the analyses does not distinguish between screen-detected cancers and non-screen-detected cancers in the screening group. Numbers in *Italic* were not reported by the authors but derived from other data provided in the study. **Cressman et al.¹²⁴ only reported the mean cost of false positives disaggregated by sex (female: \$83, male: \$41). Abbreviations: SA = sensitivity analysis, NLST = National Lung Screening Trial, NELSON = Nederlands-Leuven Longkanker ScreeningsOnderzoek, NZ = New-Zealand, y = years, LC = Lung Cancer, mm = millimeter, Gen pop = General Population.

As described elaborately in Chapter 2.2 the evaluation of screening programmes is associated with a number of potential biases which, if not corrected for, may distort the outcomes and results of the evaluation. **Lead-time bias** means that screening will lead to earlier diagnosis, but the time of death may occur at the same time as without the screening. This means that patients would not live longer due to screening but are only longer aware that they have cancer. The presence of this type of bias would mean an overestimation of the (cost-)effectiveness of the screening programme. Unfortunately, only a minority of the included studies (6/23) addressed the issue of lead-time bias in their models.^{116, 135, 139-142} Veronesi et al.¹⁴² corrected for lead-time bias by adding two years (i.e., the lead-time) to the life years of the lung cancer cases in the usual care arm. Griffin et al.¹³⁹ and UK NSC¹¹⁶ reported that the ENaBL model already inherently adjusts for lead-time bias. UK NSC¹¹⁶ reported lead time as an output of their model, which ranged between 4.07 and 8.63 months for the scenarios on the cost-effectiveness frontier. In general, the average lead time in the single-screening arms was 0.34 years, 0.57 years in the triple screening arms, 0.75 years in annual screening, and 0.67 years in the biennial screening arms. Sun et al.¹³⁵ reported accounting for lead-time bias with a lead-time of 1 year, but did not describe the approach they followed. In contrast, Jaine et al.¹⁴⁰ and McLeod et al.¹⁴¹ both opted for a lead-time of 0.5 years. Three studies varied the lead-time in the sensitivity analyses, concluding that lead-time bias has a moderate to substantial effect on the cost-effectiveness of lung cancer screening.¹⁴⁰⁻¹⁴² The remaining studies either explicitly reported not

taking into account lead-time bias as a limitation (3/23) or did not report on lead-time bias (14/23). A second potential source of bias in the cost-effectiveness estimates of the included studies is **length bias**, which may distort patient survival due to screening mostly detecting the slower progressing tumours while the rapidly progressing tumours might reach the clinical diagnosis stage more quickly and are therefore not picked up by the screening programme. It can be considered as an extreme form of overdiagnosis.¹¹¹ Only two of the included studies reported adjusting for length bias.^{116, 139} Both studies are based on the ENaBL model, which already corrects inherently for these types of bias according to the authors.

The third type of bias, which can also be considered as a potential harm of screening, is **overdiagnosis**. Overdiagnosed cancers are those (often small and slow-growing) cancers detected by the screening programme that would never have become symptomatic over the patient's remaining life span. By detecting these overdiagnosed cancers, unnecessary, but costly diagnostic procedures and treatments are performed without additional health benefits compared to a no-screening situation. Both these procedures as well as the potential complications could be considered as harms of screening. Despite the relevance of overdiagnosis, less than half of the included studies (11/23) adjusted for the effect of overdiagnosis on the cost-effectiveness of lung cancer screening.^{116, 122, 128-130, 134-136, 139-141} The remaining studies either explicitly assumed an overdiagnosis rate of 0% (1/23)¹⁴², reported not taking into account overdiagnosis (2/23)^{123, 133}, or did not report overdiagnosis at all (9/23). Reported non-zero overdiagnosis rates ranged between 1.9% and



31% and were mainly based on trial data (e.g., NLST, NELSON) or previously published literature. The handling of overdiagnosis differed between the various studies. Behar Harpaz et al.¹²² multiplied the number of diagnosed cases in the screening arms by a constant factor to account for overdiagnosis and based the magnitude of the constant factor on the NLST and NELSON trials, but they had to recalculate the overdiagnosis rate to fit their model. In addition, they assumed all overdiagnosed cases to be stage I lung cancers and all of them to survive lung cancer. Three studies based themselves on the NLST for the magnitude of overdiagnosis but did not provide detailed information on how overdiagnosis was incorporated into their model.¹²⁸⁻¹³⁰ Esmaeili et al.¹³⁴, who based their overdiagnosis rate on two meta-analyses, assumed that all the overdiagnosed cases in the first year are treated in the same way as the patients for whom the treatment is necessary and their progression to death was assumed to be like the normal pattern of mortality in the general population. Toumazis et al.¹³⁶ made use of a CISNET model and reported overdiagnosis as an outcome rather than an input of the model. Griffin et al.¹³⁹ and UK NSC¹¹⁶ argue the ENaBL model they use already takes into account overdiagnosis by making the assumption that if detection occurred earlier but at the same cancer stage, then no survival benefit was gained. This assumption should also adjust for the previously discussed lead-time bias and length bias according to the authors. While Sun et al.¹³⁵ did assume a 0% overdiagnosis rate in the base case analysis, they did vary the overdiagnosis rate between 0% and 20% in the sensitivity analyses based on Australian data. While the authors discussed the implications of higher overdiagnosis rates on costs and health outcomes, they failed to provide the approach they followed to incorporate overdiagnosis in their model. McLeod et al.¹⁴¹ included overdiagnosis in their evaluation by removing 8.9% (based on NELSON) of screen-detected local stage cancers in the LDCT arm. Finally, Jaine et al.¹⁴⁰ claim removing the effect of overdiagnosis in the NLST arms (i.e., LDCT and CXR) prior to modelling the stage shift with a two-step stage shift process. Only a quarter of the studies accounting for overdiagnosis (4/11), varied the rate of overdiagnosis in the sensitivity analyses to estimate its impact on the cost-effectiveness of the proposed lung cancer screening programme.^{128, 130, 134, 135} However, all studies concluded that the rate of overdiagnosis due to the screening programme has a substantial effect on the cost-effectiveness of that screening programme.

Another characteristic of lung cancer screening programmes is that not every result is clear-cut positive or negative but may be inconclusive. These **indeterminate results** require further (diagnostic) testing and may therefore increase costs as well as worsen health outcomes due to potential adverse events associated with these additional procedures. Only a handful of studies (5/23) reported incorporating the impact of indeterminate findings in their evaluation.^{116, 122, 127, 139, 142} While Nagy et al.¹²⁷ only took into account a temporary disutility of 0.0345 for three months to participants with an indeterminate result, Veronesi et al.¹⁴² and UK NSC¹¹⁶ only assigned an additional cost of follow-up to these participants. Behar Harpaz et al.¹²² and Griffin et al.¹³⁹ are the only studies assigning both the costs of additional follow-up and a temporary disutility to indeterminate cases. Griffin et al.¹³⁹ used the same values as in the case of a false positive: a disutility of 0.063 for three months and a cost of £184.63. Behar Harpaz et al.¹²² opted for a smaller disutility of 0.02 for the same time period (i.e., three months) and the cost of a follow-up CT scan.

During LDCT screening it is possible that other diseases than lung cancer are identified. These **incidental findings** most often require a referral to other physicians and subsequently a suited treatment. While there is consensus that incidental findings lead to additional costs related to the diagnosis and treatment of the disease on the short term, it is possible, depending on the detected disease, that more substantial costs due to more extensive procedures are avoided on the longer term. In terms of health gains, substantial uncertainty remains on the extent to which incidental findings lead to additional health gains or losses. As described elaborately in previous chapters, the topic of incidental findings is difficult with a lack of high-quality evidence. Two included studies considered the effect of incidental findings on the cost-effectiveness of lung cancer screening.^{124, 140} Jaine et al.¹⁴⁰ accounted for the additional cost of incidental findings on the short term by assigning the cost of one additional imaging test and one additional specialist consultation. Cressman et al.¹²⁴ examined the impact of taking into account the potential health benefits from incidental coronary findings by lowering the mortality by 10% in a scenario analysis. The remaining studies either explicitly or implicitly did not include incidental findings in their analyses.



Key points

Screening participation & adherence

- Most studies either explicitly or implicitly assumed an unrealistic participation (13/23) of 100% in their analyses.
- The assumed participation rate in studies reporting a non-100% participation rate ranged between 15% and 84%, with half of this selection of studies (4/9 studies) opting for a rate below 50%.
- Approximately half of the studies reported an adherence rate, but only five studies reported an adherence rate below 100%. The assumed adherence rate in studies reporting a non-100% adherence rate ranged between 70% and 95%, with the exception of Yuan et al. assuming an adherence rate of 35.32%.^m
- A minority of studies included participation and/or adherence rate in the sensitivity analyses.

Sensitivity & specificity

- Approximately half of the included studies (17/23) (indirectly) reported LDCT screening sensitivity and/or specificity. However, the sensitivity and specificity rates differed greatly across the various studies.
- The reported sensitivity of LDCT screening in the selected studies ranges from 60% to 99.9%. The reported specificity is situated between 47% and 100%.

False positives & false negatives

- Most studies incorporating the rate of false positive screens took into account an additional cost for false positives. Considerable variation in the magnitude of the costs was observed. Half of the studies

incorporating a cost for false positives additionally assigned a temporary disutility to false positive screens.

- In the case of false negatives, studies either assigned zero treatment and diagnostic costs to false negative screens, assumed these were found in the next screening round, assigned a specific cost to a false negative screen, or assumed the same clinical stage distribution of non-screened individuals.
- Overall, only a minority of studies specified how false positives and/or false negatives were handled.

Lead-time & length bias

- The large majority of studies did not address the issue of lead-time (17/23) and/or length bias (21/23).
- The studies correcting for lead-time bias used lead times between 0.5 and 2 years.
- UK NSC¹¹⁶ and Griffin et al.¹³⁹ argue the model (i.e., ENaBL) they use inherently corrects for both lead-time and length bias.

Overdiagnosis

- Less than half of the included studies (11/23) accounted for overdiagnosis as a consequence of the proposed lung cancer screening programme.
- The percentages of overdiagnosis used in the base case amounted between 0% and 31%.

^m Yuan et al.¹²⁸ refers to an adherence rate of 35.32%, but it is unclear whether this percentage was used as a participation rate or adherence rate in the analyses.



- A third of the studies accounting for overdiagnosis varied overdiagnosis rates in the sensitivity analyses with all finding a substantial impact on the ICERⁿ.

Indeterminate results & incidental findings

- Only a handful of studies (5/23) reported handling indeterminate findings. This was achieved by assigning a cost and/or disutility to indeterminate findings.
- Only two studies took incidental findings into account to a certain extent. While Jaine et al.¹⁴⁰ assigned an additional cost to incidental findings, Cressman et al.¹²⁴ took into account additional health gains from the incidental findings.

4.3. Results of economic evaluations on lung cancer screening programmes

While Section 4.2 focused on providing an overview of the various methodological approaches used in each of the included studies, this section summarizes and discusses the results of the included studies. First, the base case results will be summarized in Section 4.3.1 after which the results of the sensitivity analyses will be discussed in Section 4.3.2.

4.3.1. Base case results

Table 18 summarizes the key results of the included primary economic evaluations for the base case analyses only. In case a study did not put forward a clear base case, ranges were reported as well as the results of the scenario resulting in the lowest ICER. As discussed previously, 19 of the 23 included studies compared an LDCT lung cancer screening programme

to a situation without lung cancer screening, which reflects the current Belgian situation. **Incremental costs** due to the proposed lung cancer screening programme per screen-eligible candidate ranges between £17 (~€20) and NZ\$ 4193 (~€2359). The **incremental health benefits** were expressed using two different outcomes: 1 study solely expressed the health outcomes as life-years gained (LYG), 15 studies used quality-adjusted life years (QALYs), and three studies expressed the health outcomes in both LYG and QALYs (i.e., without and with correction for quality of life). The reported LYG due to lung cancer screening ranged between 0.025 and 0.09 LYG. The reported QALYs gained on the other hand are situated between 0.00002 and 0.1257. The resulting **ICERs** of the examined lung cancer screening programmes in this selection of included studies vary between £1529 (~€1772)/QALY gained and US\$5 943 556 (~€5 573 628)/QALY gained in the base case analyses. Without taking the outlier of Zeng et al.¹³⁰ (i.e., US\$5 943 556) into consideration the range of the ICERs translates to £1529 (~€1772)/QALY gained – CA\$92 025 (~€63 269)/QALY gained. Of the 18 studies reporting the ICER in terms of incremental cost/QALY gained, 13 studies found an ICER below €35 000/QALY gained, two studies an ICER above €35 000/QALY gained, and three studies resulted in an ICER with a lower limit below and an upper limit above €35 000/QALY gained. In other words, all included primary economic evaluations find that implementing a lung cancer screening programme leads to additional costs for the healthcare system as well as additional health gains in terms of LYG and QALYs. However, the magnitude of both the incremental costs and health gains varies considerably between the included studies. With the exception of Jaine et al.¹⁴⁰ and IHE¹¹⁸, all studies concluded that introducing a lung cancer screening programme is (likely to be) cost-effective. The full conclusions of each of the included studies are available in Table 116 in the appendix.

ⁿ A substantial impact on the ICER was defined as a 20% change or more in the ICER.


Table 21 – Cost-effectiveness results in academic publications (2020-2023) & HTAs

Study	Intervention	Comparator	Screening strategy	Incremental costs	Incremental benefits	ICER	Deemed cost-effective by authors?
Academic publications							
Behar Harpaz, 2023 ¹²²	LDCT screening	No screening	NLST: screening in years 0, 1, 2 with NLST eligibility criteria NELSON: screening in years 0, 1, 3, 5 with NELSON eligibility criteria	NLST: AU\$1434 NELSON: AU\$1606	NLST: 0.019 QALYs gained 0.038 LYG NELSON: 0.041 QALYs gained 0.067 LYG	NLST: AU\$76 300/QALY gained AU\$38 250/LYG NELSON: AU\$39 250/QALY gained AU\$24 050/LYG	Yes
Al Khayat, 2022 ¹²³	LDCT screening	No screening	Annual screening for current or former smokers aged 50-60 with NELSON smoking history	€46.67	0.003 QALYs gained	€14 094/QALY gained	Yes
Cressman, 2022 ¹²⁴	LDCT screening with PLCO _{m2012}	LDCT screening with USPSTF-2013 eligibility criteria	Screening in years 0 and 2 with PLCO _{m2012} or USPSTF eligibility criteria	- US\$355	0.20 QALYs gained	cost saving	Yes
Gomez-Carballo, 2022 ¹²⁵	LDCT screening	No screening	Screening in years 0, 1, 3 with NELSON eligibility criteria	€59*	0.024 LYG* 0.025 QALYs gained*	€2425/LYG €2345/QALY gained	Yes
Kim, 2022 ¹²⁶	LDCT screening	No screening	Annual screening for current or former smokers aged 55-74 with ≥30 PY	US\$1817.10	0.072 QALYs gained	US\$25 383/QALY gained	Yes
Nagy, 2022 ¹²⁷	LDCT screening	No screening	Annual screening for current smokers aged 55-74 with ≥20 PY	€176	0.03 QALYs gained	€5707/QALY gained	Possibly



Study	Intervention	Comparator	Screening strategy	Incremental costs	Incremental benefits	ICER	Deemed cost-effective by authors?
			Biennial screening for current smokers aged 55-74 with ≥ 20 PY	€119	0.01 QALYs gained	€10 203/QALY gained	
Yuan, 2022a ¹²⁸	LDCT screening	No screening	Annual screening for current or former smokers aged 50-74 with ≥ 30 PY and < 15 y since quitting	Not reported (estimated at US\$450)	Not reported (estimated at 0.035 QALYs gained)	US\$12 547/QALY gained	Yes
	LDCT screening with smoking cessation (individual counselling + pharmacotherapy)	No screening	Annual screening for current or former smokers aged 45-74 with ≥ 20 PY and < 15 y since quitting	Not reported (estimated at US\$134)	Not reported (estimated at 0.0303 QALYs gained)	Not reported (estimated at US\$4422/QALY gained)	
Yuan, 2022b ¹²⁹	LDCT screening with smoking cessation (individual counselling + pharmacotherapy)	LDCT screening without smoking cessation intervention	Annual screening for current or former smokers aged 45-74 with ≥ 20 PY and < 15 y since quitting	Not reported	Not reported	Not reported	Yes
	LDCT without smoking cessation intervention	No screening	Annual screening for current or former smokers aged 55-74 with ≥ 20 PY and < 15 y since quitting	Not reported (estimated at US\$81)	Not reported (estimated at 0.013 QALYs gained)	Not reported (estimated at US\$6230/QALY gained)	
Zeng, 2022 ¹³⁰	LDCT screening	No screening	Multiple scenarios for interval: One-off, annual, biennial, 5 years, 10 years, 20 years Multiple scenarios for start age: 30, 35, 40, 45, 50	Male cohort: US\$26 - US\$1301 Female cohort: US\$27 - US\$1322	Male cohort: 0.00002 – 0.02447 QALYs gained Female cohort: 0.00001 – 0.01138 QALYs gained	Male cohort: US\$16 086- US\$3 675 491/QALY gained Female cohort: US\$36 624- US\$5 943 556/QALY gained	Yes



Study	Intervention	Comparator	Screening strategy	Incremental costs	Incremental benefits	ICER	Deemed cost-effective by authors?
			<u>Lowest ICER (fe)male cohorts:</u> annual screening for current or former smokers aged 50-79	Male cohort: Lowest ICER: US\$369 Female cohort: Lowest ICER: US\$383	Male cohort: Lowest ICER: 0.02292 QALYs gained Female cohort: Lowest ICER: 0.01046 QALYs gained	Male cohort: Lowest ICER: US\$16 086/QALY gained Female cohort: Lowest ICER: US\$36 624/QALY gained	
Zhao, 2022 ¹³¹	LDCT screening	No screening	One-off screening of current smokers aged 65-74 with ≥20 PY	CNY4872.10	0.037 QALYs gained	CNY131 284.57/QALY gained	Yes
			Annual screening of current smokers aged 55-74 ≥20 PY	CNY7963.9	0.041 QALYs gained	CNY192 119.62/QALY gained	
Cadham, 2021 ¹³²	Smoking cessation interventions with LDCT screening	LDCT screening without smoking cessation intervention	Annual screening for current or former smokers aged 55-80 with ≥30 PY and <15y since quitting	US\$4.55 – US\$52.64	0.00660 – 0.01001 QALYs gained	US\$555 – US\$5258/QALY gained	Yes
	<u>Lowest ICER:</u> screening + electronic/web counselling + pharmacotherapy	<u>Lowest ICER:</u> LDCT screening without smoking cessation intervention	Annual screening for current or former smokers aged 55-80 with ≥30 PY and <15y since quitting	<u>Lowest ICER:</u> US\$4.55	<u>Lowest ICER:</u> 0.0082 QALYs gained	<u>Lowest ICER:</u> US\$555/QALY gained	
Diaz, 2021 ¹³³	LDCT screening	No screening	One-off screening at 55y for current or former male smokers aged 55-65 with ≥30PY	€98	0.00564 QALYs gained	€17 352/QALY gained	Yes
	LDCT screening with smoking	No screening	Triennial screening for current or former male	€191	0.04032 QALYs gained	€4732/QALY gained	



Study	Intervention	Comparator	Screening strategy	Incremental costs	Incremental benefits	ICER	Deemed cost-effective by authors?
	cessation (3 rounds intensive intervention)		smokers aged 55-65 with ≥30PY				
Esmaeili, 2021 ¹³⁴	LDCT screening	No screening	Triennial screening for current or former smokers aged 55-74 with 13-38 PY	IRR 2 681 590.821 €59.09	0.02722 QALYs gained	IRR 98 515 014.04/QALY gained €2174/QALY gained	Yes
Sun, 2021 ¹³⁵	LDCT screening	No screening	Annual screening for current smokers with ≥20PY Multiple scenarios for start age: 40, 45, 50, 55, 60 Stop age: 76	US\$1085 – US\$1922.5	0.0805-0.1222 QALYs gained	US\$13 056.82- US\$15 736.06/QALY gained	Likely
			Lowest ICER: Annual screening for current smokers aged 55-76 with ≥20PY	US\$1326.6	0.1016 QALYs gained	US\$13 056.82/QALY gained	
Toumazis, 2021 ¹³⁶	LDCT screening with USPSTF2021 criteria	LDCT screening with USPSTF2013 criteria	Annual screening for current or former smokers aged 50-80 with ≥20PY and <15y since quitting vs. Annual screening for current or former smokers aged 55-80 with ≥30PY and <15y since quitting	US\$49.59	0.000683 QALYs gained	US\$72 564/QALY gained	Yes
Du, 2020 ¹³⁷	LDCT screening	No screening	Annual screening for current smokers aged 50-75	<u>Men</u> : €2603 <u>Women</u> : €2622	<u>Men</u> : 0.08279 LYG <u>Women</u> : 0.08479 LYG	<u>Men</u> : €31 400/LYG <u>Women</u> : €30 900/LYG	Yes



Study	Intervention	Comparator	Screening strategy	Incremental costs	Incremental benefits	ICER	Deemed cost-effective by authors?
Evans, 2020 ¹³⁸	LDCT screening with smoking cessation intervention	LDCT screening without smoking cessation intervention	Annual screening for current or former smokers aged 55-74 with ≥30 PY and <15y since quitting	CA\$2200	0.098 QALYs gained (0.13 LYG)	CA\$22 200/QALY gained	Likely
Griffin, 2020 ¹³⁹	LDCT screening	No screening	Scenarios for interval: One-off, triple screen, biennial, annual Scenarios for start and stop age between 55-80	£23 - £48	0.00082 – 0.00122 QALYs gained	£28 169-£40 034/QALY gained	Possibly
			Lowest ICER: single screen for current or former smokers aged 60-75 with a risk of LC >3%	Lowest ICER: £23	Lowest ICER: 0.00082 QALYs gained	Lowest ICER: £28 169/QALYs gained	
Jaine, 2020 ¹⁴⁰	LDCT screening	No screening	Biennial screening for 20 years for current or former smokers aged 55-74 with ≥30 PY and <15y since quitting	NZ\$4193	0.0677 QALYs gained	NZ\$65 000/QALY gained	Unlikely
McLeod, 2020 ¹⁴¹	LDCT screening	No screening	Biennial screening for current or former smokers aged 55-74 with ≥30 PY and <15y since quitting	NZ\$4088	0.1257 HALYs gained	NZ\$34 400/HALY gained	Likely
Veronesi, 2020 ¹⁴²	LDCT screening	No screening	Annual screening for 5y for current or former smokers aged 55-79 with ≥30 PY and <15y since quitting	€254.94	0.08 QALYs gained 0.09 LYG	€3297/QALY gained €2944/LYG	Yes



Study	Intervention	Comparator	Screening strategy	Incremental costs	Incremental benefits	ICER	Deemed cost-effective by authors?
Health Technology Assessments (HTAs)							
UK NSC, 2022b ¹¹⁶	LDCT screening	No screening	Multiple scenarios for interval: single screen, triple screen, annual, biennial	£17 - £39	0.011 QALYs gained – 0.029 QALYs gained	£1529 - £4385/QALY gained	Likely
			Multiple scenarios for start age (55 or 60) and stop age (75 or 80) Multiple scenarios for risk threshold: 3%, 4%, 5%				
IHE, 2014 ¹¹⁸	LDCT screening	No screening	Lowest ICER: single screen for current or former smokers aged 55-75 with LLPv2 >4%	Lowest ICER: £17	Lowest ICER: 0.011 QALYs gained	Lowest ICER: £1529/QALY gained	Unlikely
			Screening for current or former smokers aged 55-75 with ≥30 PY	CA\$705.82 - CA\$1234.17	0.0105 QALYs gained – 0.0134 QALYs gained	CA\$67 396 - CA\$92 025/QALY gained	
			Lowest ICER: biennial screening for current or former smokers aged 55-75 with ≥30 PY	Lowest ICER: CA\$705.82	Lowest ICER: 0.0105 QALYs gained	Lowest ICER: CA\$67 396/QALY gained	

*Note: Indicative currency exchange rates on 31/05/2023: AU\$1 = €0.61; US\$1 = €0.94; CNY1 = €0.13; IRR1 = €0.000022; £1 = €1.16; NZ\$1 = €0.56; CA\$1 = €0.69. Values in italic were based on own calculations. *Recalculated from incremental cost or effect/lung cancer patient to incremental cost or effect/screened individual by Behr et al.¹⁴⁸*

Abbreviations: LDCT = Low-Dose Chest Computer Tomography, NLST = National Lung Screening Trial, NELSON = Nederlands-Leuven Longkanker ScreeningsOnderzoek, LYG = Life Years Gained, QALY = Quality-Adjusted Life Year, PY = Pack Years, y = years, ICER = Incremental Cost-Effectiveness Ratio, USPSTF = United States Preventive Services Task Force, HALY = Health-Adjusted Life Year, LC = Lung Cancer, IRR = Iranian Rial, CNY = Chinese Yuan Renmibi, US\$ = American Dollar, AU\$ = Australian Dollar, CA\$ = Canadian Dollar, £ = Pound Sterling, NZ\$ = New Zealand Dollar.



A second set of economic evaluations was specifically aimed at examining the **cost-effectiveness of integrating a smoking cessation programme** into a lung cancer screening programme.^{129, 132, 133, 138} Two studies compared lung cancer screening with a smoking cessation programme to a situation without lung cancer screening. Yuan et al.¹²⁹ added individual counselling and pharmacotherapy to lung cancer screening, which resulted in 0.0303 QALYs gained at an additional cost of US\$134 (~€126) and subsequently an ICER of US\$4422 (~€4147)/QALY gained^o. Diaz et al.¹³³ examined the cost-effectiveness of LDCT screening combined with either a brief smoking cessation intervention (5A's) or an intensive smoking cessation intervention (behavioural therapy & medication), of which the latter was considered the most cost-effective with 0.04 QALYs gained and €191 additional costs leading to an ICER of €4732/QALY gained. Both studies concluded that adding a smoking cessation programme to a lung cancer screening programme is cost-effective. The two remaining studies compared lung cancer screening with a smoking cessation intervention to lung cancer screening without smoking cessation intervention. Evans et al.¹³⁸ suggested adding nicotine replacement therapy, varenicline, and a 15 minutes counselling session per week for 12 weeks to lung cancer screening, which resulted in 0.098 QALYs gained, incremental costs of CA\$2200 (~€1513), and an ICER of CA\$22 200 (~€15 263)/QALY gained. Cadham et al.¹³² evaluated 5 different smoking cessation interventions in combination with lung cancer screening and found ICERs between US\$552 (~€521) and US\$5258 (~€4931)/QALY gained. Like the first two studies, both of these studies concluded that adding a smoking cessation intervention induces more costs for the healthcare system but increases the health benefits of the screening programme to a greater extent and was therefore also considered cost-effective by both studies. While Yuan et al.¹²⁹ did mention comparing to a situation with lung cancer screening without smoking cessation intervention, they did not report the results of these analyses sufficiently transparent in order to be reproduced in this report.

^o Yuan et al. did not provide numerical results for the incremental costs, QALYs gained, and the ICER. The reported values are based on estimations from a graphical display of results.

The final two studies had very **specific research questions related to the eligibility** for lung cancer screening. First, Cressman et al.¹²⁴ found that using the PLCom2012 risk assessment tool instead of the USPSTF-2013 eligibility criteria (based on smoking history and age) led to 0.20 QALYs gained and was above all cost-saving with incremental costs of -US\$355 (~€334). Second, Toumazis et al.¹³⁶ evaluated the cost-effectiveness of the more recent USPSTF2021 eligibility criteria to the 2013 edition. The main difference between the two editions is that the 2021 version lowered both the minimal amount of pack-years necessary to be eligible for screening (from 30 to 20) and the start age of screening (from 55 to 50). This modification resulted in 0.000683 QALYs gained at an incremental cost of US\$49.59 (~€47), leading to an ICER of US\$72 564 (~€68 048)/QALY gained.

Key points

Studies comparing a lung cancer screening programme to no lung cancer screening programme (= the current Belgian situation):

- The incremental costs of introducing a lung cancer screening programme per screen-eligible candidate range from £17 (~€20) to NZ\$4193 (€2359).
- The included studies show that organizing a lung cancer screening programme would lead to incremental health gains, ranging between 0.00002 and 0.1257 QALYs gained.
- The ICERs of studies evaluating the cost-utility of a lung cancer screening programme compared to a situation without lung cancer screening amount between £1529 (~€1772)/QALY gained and CA\$92 025 (~€63 269)/QALY gained in the base case analyses without taking the outlier of Zeng et al.¹³⁰ (US\$5 943 556) into consideration.



- With the exception of Jaine et al.¹⁴⁰ and IHE¹¹⁸, all studies concluded that introducing a lung cancer screening programme is (likely to be) cost-effective.

Studies evaluating the cost-effectiveness of adding a smoking cessation intervention to lung cancer screening:

- All studies concluded adding a smoking cessation intervention to lung cancer screening was cost-effective.
- The studies examining the cost-effectiveness of screening with or without smoking cessation intervention all concluded that lung cancer screening programmes with smoking cessation intervention(s) are more cost-effective than screening programmes without smoking cessation interventions.

Remaining studies:

- The study of Cressman et al.¹²⁴ concluded that using the risk assessment tool PLCom2012 instead of the USPSTF-2013 eligibility criteria resulted in additional health gains and cost savings.
- Toumazis et al.¹³⁶ evaluated the cost-effectiveness of the more recent and broader USPSTF-2021 eligibility criteria compared to the older and more confined USPSTF-2013 eligibility criteria. The authors found an ICER of US\$72 564 (€68 048)/QALY gained.

4.3.2. Sensitivity analyses

As a fundamental part of every health economic evaluation, the sensitivity analyses give more insight into the uncertainty in the cost-effectiveness estimates as well as which variables are most influential on the incremental cost-effectiveness ratio (ICER). Six of the 23 included studies only performed deterministic sensitivity analyses^{118, 126, 131, 132, 135, 137}, of which four^{118, 126, 131, 137} only conducted univariate sensitivity analyses and two^{132, 135} opted for both uni- and multivariate sensitivity analyses. Yuan et al.¹²⁹ is the only study conducting solely probabilistic sensitivity analyses. The remaining studies (16/23) performed and reported both deterministic and probabilistic sensitivity analyses.

The variables included in the sensitivity analyses of each included study are summarized in Appendix Table 115 with an indication (variables in bold) of whether the variable had a substantial impact on the ICER or not. Currently no guidelines on what is considered to be a substantial impact are available in the literature. Therefore, a cut-off value of 20% was chosen. This means that, wherever possible, the impact of individual parameters was calculated and changes in parameters leading to a 20% change in the ICER or more were considered to be substantial in magnitude. First, the **cost of screening**, in multiple studies incorrectly equalized to solely the cost of an LDCT screen, was found to have a substantial impact on the cost-effectiveness of lung cancer screening by nine studies.^{122, 125, 126, 132, 133, 137, 139, 140, 142}

Second, the **screening strategy** as a whole, consisting of the screening intervals as well as the eligibility criteria for screening, were identified as having a major impact of the cost-effectiveness of the evaluated lung cancer screening programmes. The studies examining the impact of the screening interval on the ICER found inconsistent results. Intuitively, moving from biennial to annual screening would result in a proportionally larger increase in incremental costs than in incremental effects. While this line of thought was confirmed by three studies^{118, 133, 137}, three studies^{126, 127, 130} identified an increase of the ICER of which one¹²⁷ even found a decrease in the QALYs gained by a factor of three. This seems rather counter-intuitive due to the magnitude of the costs related to the screening programme and their impact on the ICER in the sensitivity analyses. In two studies the biennial screening strategy was dominated by other strategies.^{116, 139} The same inconsistent



findings apply to the studies examining the impact of moving from an annual screening frequency to a single screen, where two studies^{130, 131} found an increase and three a decrease in the ICER.^{116, 133, 139} As discussed previously, a considerable amount of studies also varied the start & stop ages of the eligibility criteria for screening in the sensitivity and/or scenario analyses. With regard to age, the results are more consistent. The majority of studies (8/11) found that increasing the starting age for screening, *ceteris paribus*, leads to a decrease in the ICER.^{116, 126, 127, 129-131, 137, 139} In contrast, only one study concluded that lowering the lower age limit for screening would render the screening programme less cost-effective.¹²³ The two remaining studies found decreasing ICERs with increasing starting ages until a ceiling was hit after which the ICER increased (i.e., from 55-76 → 60-76 and 65-74 → 70-74).^{128, 135} Increasing the upper age limit for screening, *ceteris paribus*, resulted in an increase of the ICER in four studies. In the study of Du et al.¹³⁷, the ICER first decreased when shifting the age eligibility criteria from 55-75 to 55-80 after which the ICER increased when further increasing the upper age limit. Two studies also examined the effect of increasing the whole age eligibility criteria (start & stop age simultaneously) and both found a decrease in the ICERs. A limited number of studies also investigated the impact of the smoking history eligibility criteria on the cost-effectiveness of lung cancer screening. Jaine et al.¹⁴⁰ for example ran a scenario analysis for current smokers only and found a very small decrease (i.e., 3%) in the ICER. Nagy et al.¹²⁷ broadened the screen-eligible population from current smokers to the general population in a scenario analysis, which was associated with an increase in the ICER. Yuan et al.¹²⁸ increased the number of minimally necessary pack years to be eligible for screening from 20 to 25, which rendered the screening programme more cost-effective. Toumazis et al.¹³⁶ relaxed the smoking cessation criteria by increasing the maximal number of years since quitting from 15 to 20 years, which increased the ICER. The two UK-based studies used a risk assessment tool to define the high-risk population. In their sensitivity analyses, the screening programme became less cost-effective when the risk thresholds were increased from 3% to 4% and 5%.^{116, 139}

Multiple of the previously discussed **screening-specific factors** (see Table 20) were found to have a substantial impact on the cost-effectiveness of the lung cancer screening programme. Increasing the overdiagnosis rate^{128, 130, 134, 135} or lowering the screening participation rate^{116, 121, 125, 132, 133}, the sensitivity^{133, 135} or specificity^{140, 142} of screening were associated with a substantial increase in the ICER by multiple studies, rendering the lung cancer screening programme less cost-effective. These results further stress the importance and necessity of incorporating these variables and correcting for these sources of bias to obtain a correct, realistic estimation of the cost-effectiveness of a lung cancer screening programme. Due to the lack of transparency in the handling of these factors by multiple studies, there is still some uncertainty around the true impact of these factors. However, previously published HTAs and systematic reviews confirm their potentially substantial impact on the cost-effectiveness of LCS.^{111, 113, 114} As discussed previously, the remaining screening-specific factors of Table 20 were rarely included in sensitivity analyses. The lead time was varied in only three studies, which considered the impact of the lead time on the ICER to be moderate to substantial but below our pre-defined cut-off value. Indeterminate results, length bias, and incidental findings were not incorporated in the sensitivity analyses of the included studies, meaning that the impact of these variables on the cost-effectiveness remains unclear.

Other factors with substantial impacts on the ICER were the health utility of stage I or localized lung cancer (-), cost of stage IV lung cancer or non-curative treatment (-), discount rates (+), and the cost of diagnosis (+), with '-' indicating a decrease in the ICER when the respective factor increases and '+' an increase in the ICER when the respective factor increases. Furthermore, some variables were only found to have a substantial impact on the ICER by individual studies: life expectancy in stage I (-), cost of lung cancer treatment in stages I-III (+), post-diagnosis cost (+), incidence of heavy smokers (-), distribution over lung cancer stages, positive screening rate (-), disutilities of screening and follow-up (+), and the mortality benefit resulting from screening (-).^P Finally, only three studies varied the time horizon over which health effects and costs were modelled in the sensitivity

^P '-' indicates that the ICER decreases when the respective factor increases.
'+' indicates that the ICER increases when the respective factor increases.



analysis. Behar Harpaz et al.¹²² changed the time horizon from a lifetime horizon to a time horizon of 20 years, resulting in a 12% and 14% increase in the ICERs of the NLST and NELSON scenarios respectively. UK NSC¹¹⁶ used a similar approach and ran a simulation for a 10-year time horizon instead of a lifetime horizon (typically 15 life years in their base case model). However, they did not find any change in the cost-effectiveness due to this change in time horizon. Gomez-Carballo et al.¹²⁵ performed scenario analyses for 5- and 10-year time horizons, which led to contradictory results with the ICER increasing slightly in the first scenario (by 4%) and decreasing in the latter scenario (by 9%). Unfortunately, the authors did not provide an explanation for these findings.

Key points

The most influential factors on the ICER were identified to be:

- Cost of LDCT screen
- Criteria related to the screening strategy (start & stop ages, smoking history, screening interval)
- Overdiagnosis rate
- Screening participation/coverage
- Health utility of lung cancer stage I/localized lung cancer
- Cost of stage IV/non-curative treatment
- Discount rates
- Sensitivity of screening
- Specificity of screening
- Cost of diagnosis

5. BELGIAN DATA PROCESSING

5.1. Data source : BCR – IMA – AIM database

The study population was identified in the nationwide population-based Belgian Cancer Registry (BCR) data, linked to the Inter-mutualistic Agency (IMA – AIM) data (see Box 2). Since 2009, the Belgian Cancer Registry is authorized to link data from its database with data on reimbursed cancer-related diagnostic and therapeutic procedures and pharmaceuticals (in-hospital as well as out-hospital).²²¹

Box 2 – Data sources

The linked BCR - IMA – AIM database is fed by three data sources:

1) **The Belgian Cancer Registry (BCR) data** covers all newly diagnosed cancer cases in Belgium. Completeness of incidence has been estimated to be at least 98% of all cancer cases in Belgium from 2004 onwards.²²² Information that must be legally transmitted by the hospitals and pathology laboratories include, among others, patient sex, age at diagnosis, WHO performance status, tumour incidence date (i.e., the date of first histopathological confirmation of the tumour or, if not available, the date of the technical procedure or clinical investigation leading to the diagnosis of cancer), topography and histology of the tumour (ICD-O-3), and clinical and pathological TNM stage at diagnosis (UICC TNM 5th edition for incidence years 1999-2002; 6th edition for incidence years 2003-2009; 7th edition for incidence years 2010-2016; 8th edition as from incidence year 2017 onwards).

2) **The IMA – AIM data** are managed by the Inter-mutualistic Agency ("InterMutualistisch Agentschap – Agence InterMutualiste" – IMA – AIM) and include all reimbursed services related to the compulsory national health insurance, collected by the Belgian sickness funds on all insured citizens. Services include consultations, pharmaceuticals, diagnostic and therapeutic procedures, implants and invasive medical devices, etc., in ambulatory as well as in health facilities setting (hospitals, nursing homes, etc.). These data also contains the patient's share as well as some supplements supported by the patient. Note that procedures performed



within the context of clinical trials are not (routinely) invoiced and hence not included in the IMA – AIM data.

3) The individual vital status is transmitted by **the Crossroads Bank for Social Security** ('Kruispuntbank van de Sociale Zekerheid' – 'Banque Carrefour de la Sécurité Sociale', KSZ-BCSS).

Thanks to a unique patient identifier (the National Number), each cancer case can be linked to the patient's reimbursements, patient payments, and vital status. The reimbursements span from one year before the year of diagnosis in the BCR data until 5 years afterwards. Some reimbursed services are not transmitted by the IMA – AIM to be linked to the BCR data, such as the services provided by the dentists, the physiotherapists (except palliative care), the speech therapies, the psychotherapies, the clinical biology interventions (except the tumour markers), some protheses, etc. At the time of data extraction, the linked IMA – AIM data were available until 30th June 2022 and the vital status until 1st April 2023.

5.2. Methods

5.2.1. Data privacy

Data were made available to the KCE on a secure remote server accessible from the KCE via a virtual private network from end of November 2023. Only the project's data analyst received a multi-factor authentication access to the data. The results of the data analyses were examined by the BCR before transmission to the KCE team in order to eliminate any risk of individual identification ('small cells risk analysis').

5.2.2. Data selection

A primary data extraction by the BCR included lung cancers that were diagnosed between 1 January 2015 and 31 December 2020, in patients aged between 50 and 79 years with an official residence in Belgium at the time of diagnosis and for whom no other invasive lung cancer was diagnosed between 2004 and 2014 as they would not be candidates for lung cancer screening. Tumour selection criterion was ICD-O C34 *Malignant neoplasm of bronchus and lung*. Finally patients for whom no national number was known at BCR or no link was found in the IMA – AIM data were not retained in the primary selection.

The selection was then refined to exclude patients with multiple lung cancers in 2015-2020 but younger than 50 years for the first tumour as well as bedbound patients (WHO performance status:"4"), benign tumours and finally patients who had any other cancer between 2004 and the lung cancer incidence datum. Patients with WHO performance status 4 were excluded as these patients would not be eligible for lung screening when a screening would be implemented. As IMA-AIM data have no direct link with the indication for the intervention, patients who had any other type of cancer prior to the diagnosis of lung cancer were excluded to ensure procedures were related to lung cancer as much as possible.⁹ For the same reason, a

⁹ As an example, it is not possible to differentiate between radiotherapy for lung cancer and radiotherapy for another cancer with an incidence date near to the lung cancer incidence.



time frame around the incidence data was used for the diagnostic procedures. The flowchart of the selection can be found in Appendix 8.

The total number of patients obtained was 32 832 patients, from whom 27 421 patients aged between 50 and 74 years.

5.2.3. Data analyses

5.2.3.1. Definitions

The analyses were run on a subgroup of 27 421 patients in the same age category as the NELSON study (i.e., 50-74 year old). Patients were grouped into subgroups by stage (I, II, III, IV or X for undefined), histology (SCLC versus NSCLC or others^r), and year of incidence (between 2015 and 2020).

5.2.3.2. Survival analysis

Survival probabilities were calculated according to the Kaplan-Meier method. Few patients (0.37%) were still alive and lost to follow-up after they moved abroad.

5.2.3.3. Costs calculations

For the base case scenario, the costs included the amount reimbursed by the national health insurance (IMA variable SS00060) as well as the patient's share (IMA variable SS00160). In an alternative scenario, the patient's supplements were also included (IMA variable ss00165).

Histological types other than SCLC were also grouped together (mainly NSCLC) (see Table 24). The costs include the following cost items:

- Diagnostic costs from 3 months before until 3 months after the incidence date.

- Surgical hospitalisation costs including all hospital-related costs. Hospitalisation episodes were selected based on specified surgery reimbursement codes during the episode.
- Radiotherapy costs based on specified reimbursement codes.
- Palliative care costs based on specified reimbursement codes.
- Systemic therapy costs (chemotherapy, targeted therapy, immunotherapy), including drug related costs and hospitalisation related costs. Hospitalisation episodes were selected based on specified drug related costs during that episode.
- The BCR data were also used to validate some assumptions for the follow-up period as well as determining some costs applicable to the false positive evaluations.

More details per cost item are listed below.

Costs were calculated at following dates : Day 31 (31 days after date of incidence), day 61, day 92, day 183, day 274, day 365, day 730, day 1095, day 1460, day 1825. These cut-offs amount to define the following time intervals : 1 month, 1 month, 1 month, 3 months, 3 months, 3 months, 1 year, 1 year, 1 year and 1 year, covering 5 years in total. These cut-offs were chosen in function of the evolution of survival and costs over time. Costs do not pile up linearly over a time period, cut-offs were therefore adjusted to the costs evolution so that the mean costs calculated over a period of time stayed close to the costs really charged halfway (see information on half-cycle correction in part 6.1.7).

Additionally, the diagnostic costs were also calculated for the period of 3 months preceding the date of incidence, to include the diagnostic interventions that preceded the histological confirmation of the tumour.

^r SCLC: ICD-O 8041-8045, 8246 versus NSCLC or others (8010-8040, 8046-8245, 8247-8576 or 8000, 8005, 8577-9999).



For calculation of the costs during the first month after diagnosis, the costs delivered between 7 days before incidence date were included. This additional week was included to account for possible uncertainties in the exact date of incidence or the exact date of some health care interventions.

The mean was calculated for each cost item for period T using the following formula:

$\text{Mean}_T = \sum \text{costs}_T / N_{T1/2}$, where $N_{T1/2}$ is the number of patients alive halfway through the time interval T

The denominator $N_{T1/2}$ for the ten time intervals after date of incidence was respectively the number of patients alive in the middle of the time interval at day 16, 46, 77, 1038, 229, 320, 548, 913, 1278 and 1643. For the diagnostic costs incurred in the 3 months before the date of incidence, $N_{T1/2}$ equals the number of patients alive at day 0, i.e., the total number of patients selected.

This definition of the denominator was applied to account for the loss of deceased patient over the time interval.

The standard deviation was calculated for each cost item for the time interval T using the following formula:

$\text{SD}_T = \sqrt{\sum (\text{costs}_T - \text{Mean}_T)^2 / (N_{T0} - 1)}$, where N_{T0} is the number of patients alive at the beginning of the time interval T.

Double counting of the different cost items was avoided. The RIZIV – INAMI nomenclature codes identified during the diagnostic period, as CT-scans for example, were not selected in the hospitalisation costs related to the surgery when the scan was performed during the hospitalisation. Similarly, every radiotherapy (or palliative care) code included in the palliative care (or radiotherapy) costs calculation were excluded from the surgical hospitalisation costs. Every product used in systemic therapy (and costs

billed on the day of administration) identified by its ATC code was included in the systemic therapy and was excluded from any surgical hospitalisation costs calculation.

In particular, beside the exception described above, two other costs were excluded from the surgical hospitalisation costs:

- The thorax CT performed after 3 months after incident date were not included to avoid any double counting with the thorax CT added to the model for the follow-up costs. Thorax CT are identified in bold in Appendix 9.1.2
- The pharmacist's fee in public pharmacies^s (this fee is recorded in the HEALTH IMA – AIM data file but pertains to ambulatory drug costs, recorded in FARMANET IMA – AIM data file).

Diagnostic costs

The list of RIZIV – INAMI nomenclature codes selected to define the health care interventions necessary to diagnose and stage the lung cancer can be found in Appendix 9.1. The list encompasses the multidisciplinary team meetings, the medical imaging (RX, CT, etc.), the lung function tests, the biopsies and the endoscopic techniques (bronchoscopy, EBUS, EUS, mediastinoscopy etc.).

Radiotherapy costs

All the radiotherapy-related RIZIV – INAMI nomenclature codes from Article 18.§1/A of the nomenclature^t were retained. Codes related to stereotactic body radiation therapy (SBRT) were available from 2020 onwards.

^s 753550 Basishonorarium – Honoraires de base, 753572 basishonorarium + specifiek honorarium INN – honoraires de base + honoraires spécifiques DCI, 753594 (until 2016-12-31) Basishonorarium + specifiek honorarium hoofdstuk IV – Honoraires de base + honoraires spécifiques chapitre IV, 753616 (until 2016-12-31) basishonorarium + specifiek honorarium INN +

specifiek honorarium hoofdstuk IV – Honoraires de base + honoraires spécifiques DCI + honoraires spécifiques chapitre IV.

^t Wet betreffende de verplichte verzekering voor geneeskundige verzorging en uitkeringen gecoördineerd op 14 juli 1994, B. S. 27 augustus 1994 – Loi relative à l'assurance obligatoire soins de santé et indemnités coordonnée le 14 juillet 1994, M. B. 27 août 1994.



As the data did not allow to reliably define the start and end date of radiotherapy treatment, and the absence of specific nomenclature codes for complications or side effects of radiotherapy, hospitalisation costs for possible side effects of radiotherapy were not included.

Systemic therapy costs

The costs were mostly extracted from the hospital setting (hospitalisation and day care) (HEALTH IMA – AIM data file) but also for the community setting (FARMANET IMA – AIM data file), using the list of ATC codes for chemotherapy, targeted therapy, immunotherapy presented in Appendix 9.5.

Calculations were different according to the setting:

- In hospital setting, all reimbursements and patient's shares billed on the same day of the pharmaceuticals identified were added up. Exceptions were applied, excluding some health care costs as described in the general costs calculation section above: diagnostic and staging interventions 3 months before or after incidence date, radiotherapy, palliative care, CT thorax, pharmacist's fees of public pharmacies. No correction was done for the 100% per diem price in case a lump sum was retrieved on the same day as the systemic therapy delivery. The impact of this absence of correction among the non-pharmaceutical costs in the estimation of systemic therapy costs was deemed marginal as the pharmaceutical costs represented more than 90% of the cost item.
- In community setting, reimbursements and patient's shares only for the pharmaceuticals identified were included. The pharmacist's fee in public pharmacies (recorded in the HEALTH data file but pertaining to ambulatory drug costs) recorded for these were added to the ambulatory systemic therapy costs.

Due to the administrative data's lack of specificity, costs related to side effects or complications not occurring on the day of systemic therapy administration could not be included.

Palliative costs

Palliative care codes are listed in Appendix 9.4

Surgery costs

The surgery costs were defined as the total costs of the hospitalisations during which at least one of the following surgical interventions was performed:

- Extended total or partial lung exeresis with lymph node dissection for oncological disease,
- Total or partial removal of the lung,
- Resection of a stem bronchus or trachea with anastomosis (broncho-bronchial or tracheo-bronchial) by thoracotomy.
- Thoracotomy with tentative of exeresis

Billing codes and labels are given in Appendix 9.2.

- In a first step, the day of surgery was identified. Every date of aforementioned interventions occurring between 7 days before and 5 years after incidence date were selected for each patient. In 95% of the operated patients, only one procedure was performed. The maximum number of procedures was four for one same patient (during three hospitalisations).
- The start and end dates of hospitalization matching the surgery were determined using the following cascading technique:
 - a. Variables FIRST_PREST and LAST_PREST from the hospitalisations IMA – AIM data file were first used. The matching was univoquely possible in more than 95% of the surgery dates.
 - b. In some cases, a correspondence was found in a few cases having FIRST_PREST erroneously equal to LAST_PREST when the calculated length of stay (IMA variable LOS) was added to FIRST_PREST.



- c. When no correspondence was found, the variables Admission date SS00110 and Discharge date ss00115 allowed to do the matching.
- d. Variables Admission date SS00110 and Discharge date SS00115 were also used to identify the stays during which a surgery was performed in the year 2022, as the more reliable FIRST_PREST and LAST_PREST from Hospitalisation IMA – AIM data file were only available until 31st December 2021 at the time of extraction (September 2023)^u.
- In very few cases, the surgery date was equal both to the discharge date of a first stay and the admission date of a second subsequent stay. Assuming that the patient was transferred in another hospital to be operated, both hospitalisations were collated.

Once the start and the end of the hospitalisations were known, all the costs incurred between these dates were added up, after reconstruction of the 100% per diem price.

This correction is necessary to take into account the large fixed part of the hospitals budget (budget of financial means; BFM-BFM). The fixed part of the budget is paid to the hospitals by the sickness funds in provisional twelfths and is absent from the IMA – AIM data. This part represent 80% of the 'B1-B2 components' (a.o. hospital staffing costs and standard medical material such as syringes, dressings, ...) and 100% of the other components of the budget (overheads, capital costs, ...). The variable part included in the IMA – AIM data is paid through the admission and per day lump sums. The lump sums tariffs are hospital-specific, depending on the type of bed, they are adapted and published yearly by the RIZIV — INAMI.

For this purpose, the amount reimbursed for each hospitalisation per diem lump sum was replaced by the tariff specific to each term and each hospital multiplied by the number of times the lump sums was billed. Hospitalisation lump sums per admission were discarded.

All other costs, reimbursements and patient's share, were added to the reconstructed per diem price. Exceptions were made for costs already covered by other cost items (see above: radiotherapy etc.).

As the complications after surgery requiring readmissions could not be identified in the data, these hospitalisation costs were not included.

5.2.4. Statistical and Data processing software

The analyses were performed using SAS software™ version 9.4 M5 for Microsoft Windows.²²³

5.3. Belgian results

Patients characteristics were available in the BCR data whereas health care costs were calculated on the IMA – AIM data.

5.3.1. Patient characteristics

Considering the WHO performance status 4 (bedbound) was an exclusion criteria (discarding 1.17% of the patients), the percentages of patients for each of the remaining levels in function of the patient incidence year are presented in Table 22.

^u The HOSPITALISATION file is derived by the IMA based on the original billing data. Its availability is therefore delayed compared to the original data.

**Table 22 – Patients WHO performance status per incidence year**

WHO Performance status	2015	2016	2017	2018	2019	2020	Total
0 – Asymptomatic	692 (15.5%)	698 (15.8%)	756 (16.6%)	853 (18.2%)	907 (19.6%)	847 (18.1%)	4 753 (17.3%)
1 – Symptomatic but completely ambulatory	2 673 (59.8%)	2 673 (60.6%)	2 726 (59.8%)	2 720 (58.0%)	2 779 (60.1%)	2 752 (58.9%)	16 323 (59.5%)
2 – Symptomatic, <50% in bed during the day	526 (11.8%)	473 (10.7%)	475 (10.4%)	492 (10.5%)	516 (11.2%)	640 (13.7%)	3 122 (11.4%)
3 – Symptomatic, >50% in bed, but not bedbound	178 (4.0%)	173 (3.9%)	181 (4.0%)	191 (4.1%)	213 (4.6%)	244 (5.2%)	1 180 (4.3%)
Missing	398 (8.9%)	394 (8.9%)	421 (9.2%)	430 (9.2%)	209 (4.5%)	191 (4.1%)	2 043 (7.5%)
ALL (100%)	4 467	4 411	4 559	4 686	4 624	4 674	27 421

As seen in Table 23, the staging registration quality improved as the percentage of patients staged X diminished over time (from 7.3% in 2015 to 3% in 2020).

Table 23 – Stage per incidence year

Stage	2015	2016	2017	2018	2019	2020	Total
I	730 (16.3%)	718 (16.3%)	786 (17.2%)	862 (18.4%)	887 (19.2%)	859 (18.4%)	4 842 (17.7%)
II	341 (7.6%)	339 (7.7%)	331 (7.3%)	349 (7.4%)	333 (7.2%)	318 (6.8%)	2 011 (7.3%)
III	926 (20.7%)	872 (19.8%)	935 (20.5%)	993 (21.2%)	959 (20.7%)	898 (19.2%)	5 583 (20.4%)
IV	2 146 (48.0%)	2 153 (48.8%)	2 309 (50.6%)	2 318 (49.5%)	2 327 (50.3%)	2 457 (52.6%)	13 710 (50.0%)
X	324 (7.3%)	329 (7.5%)	198 (4.3%)	164 (3.5%)	118 (2.6%)	142 (3.0%)	1 275 (4.6%)
ALL (100%)	4 467	4 411	4 559	4 686	4 624	4 674	27 421

As explained above, patients presenting another histological type than SCLC were grouped together in the subsequent analyses, representing more than 80% of all patients (Table 24).

Table 24 – Histological type per incidence year

Type	2015	2016	2017	2018	2019	2020	Total
SCLC	731 (16.4%)	669 (15.2%)	726 (15.9%)	774 (16.5%)	753 (16.3%)	758 (16.2%)	4 411 (16.1%)
NSCLC+Others	3 736 (83.6%)	3 742 (84.8%)	3 833 (84.1%)	3 912 (83.5%)	3 871 (83.7%)	3 916 (83.8%)	23 010 (83.9%)
<i>NSCLC</i>	<i>3 532 (79.1%)</i>	<i>3 551 (80.5%)</i>	<i>3 614 (79.3%)</i>	<i>3 708 (79.1%)</i>	<i>3 610 (78.1%)</i>	<i>3 648 (78.0%)</i>	<i>21 663 (79.0%)</i>



<i>Others</i>	204 (4.6%)	191 (4.3%)	219 (4.8%)	204 (4.4%)	261 (5.6%)	268 (5.7%)	1 347 (4.9%)
ALL (100%)	4 467	4 411	4 559	4 686	4 624	4 674	27 421

The proportion of SCLC tumours increased with the stage (Table 25).

Table 25 – Histological type per stage

Type	I	II	III	IV	X	Total
NSCLC+Others	4 735 (97.8%)	1 893 (94.1%)	4 567 (81.8%)	10 816 (78.9%)	999 (78.4%)	23 010 (83.9%)
SCLC	107 (2.2%)	118 (5.9%)	1 016 (18.2%)	2 894 (21.1%)	276 (21.6%)	4 411 (16.1%)
ALL (100%)	4 842	2 011	5 583	13 710	1 275	27 421

The mortality is presented per incidence year and per stage in Table 26 and Table 27. A limited number of patients were lost to follow-up when they moved their residence abroad and were reported alive at the end of their follow-up.

Table 26 – Vital status on 31 May 2023, per incidence year

Vital status	2015	2016	2017	2018	2019	2020	Total
Alive	750 (16.8%)	875 (19.8%)	1 084 (23.8%)	1 251 (26.7%)	1 520 (32.9%)	1 773 (37.9%)	7 253 (26.5%)
Dead	3 694 (82.7%)	3 526 (79.9%)	3 457 (75.8%)	3 413 (72.8%)	3 089 (66.8%)	2 888 (61.8%)	20 067 (73.2%)
Lost to follow-up	23 (0.5%)	10 (0.2%)	18 (0.4%)	22 (0.5%)	15 (0.3%)	13 (0.3%)	101 (0.4%)
ALL (100%)	4 467	4 411	4 559	4 686	4 624	4 674	27 421

Table 27 – Vital status on 31 May 2023, per stage

Vital status / stage	I	II	III	IV	X	Total
Alive	3 180 (65.7%)	952 (47.3%)	1 538 (27.5%)	1 406 (10.3%)	177 (13.9%)	7 253 (26.5%)
Dead	1 627 (33.6%)	1 046 (52.0%)	4 020 (72.0%)	12 281 (89.6%)	1 093 (85.7%)	20 067 (73.2%)
Lost to follow-up	35 (0.7%)	13 (0.6%)	25 (0.4%)	23 (0.2%)	5 (0.4%)	101 (0.4%)
ALL (100%)	4 842	2 011	5 583	13 710	1 275	27 421



The survival rates at 1, 2, 3, 4 and 5 years, calculated according to the Kaplan-Meier method, are presented in Table 28. Globally, 57% of the patients survived a year after their lung cancer diagnostic. After five years, 26.1% of them had survived. The mortality increased with the stage. The survival is

less favourable in patients diagnosed with SCLC lung cancer: after 5 years, only 9% of them survived against 29.3% of patients diagnosed with other histological types, all stages together.

Table 28 – Survival rates at 1 to 5 years

Type	Stage	1 year	2 years	3 years	4 years	5 years
NSCLC+Others	I	93.3%	86.0%	78.9%	73.5%	68.1%
	II	85.5%	72.2%	63.1%	54.6%	48.1%
	III	68.4%	50.0%	38.7%	32.1%	28.0%
	IV	38.9%	24.0%	17.3%	13.1%	10.6%
	X	40.0%	29.6%	23.6%	19.5%	17.7%
	All NSCLC+Others	59.8%	46.1%	38.3%	33.0%	29.3%
SCLC	I	85%	60.7%	45.6%	34.3%	0%
	II	80.5%	55.9%	48.2%	39.2%	34.7%
	III	66.4%	39.4%	28.5%	23.6%	21.3%
	IV	29.0%	9.9%	5.0%	3.5%	2.7%
	X	31.2%	14.1%	10.5%	8.5%	8.1%
	All SCLC	40.5%	19.4%	13.0%	10.2%	9.0%
Total		56.7%	41.8%	34.2%	29.4%	26.1%

Over the whole period, the category most affected by a diagnosis of invasive tumour was the 65-69 year-old group, even if the percentage of the last category (70-74 years) seemed to increase with time (Table 29). Most patients were male (Table 30).

**Table 29 – Age category per incidence year**

Age category	2015	2016	2017	2018	2019	2020	TOTAL
50-54 years	408 (9.1%)	425 (9.6%)	375 (8.2%)	343 (7.3%)	378 (8.2%)	330 (7.1%)	2 259 (8.2%)
55-59 years	736 (16.5%)	686 (15.6%)	686 (15.0%)	681 (14.5%)	687 (14.9%)	656 (14.0%)	4 132 (15.1%)
60-64 years	1 119 (25.1%)	1 064 (24.1%)	1 066 (23.4%)	1 072 (22.9%)	1 047 (22.6%)	1 034 (22.1%)	6 402 (23.3%)
65-69 years	1 217 (27.2%)	1 177 (26.7%)	1 246 (27.3%)	1 352 (28.9%)	1 253 (27.1%)	1 297 (27.7%)	7 542 (27.5%)
70-74 years	987 (22.1%)	1 059 (24.0%)	1 186 (26.0%)	1 238 (26.4%)	1 259 (27.2%)	1 357 (29.0%)	7 086 (25.8%)
ALL (100%)	4 467	4 411	4 559	4 686	4 624	4 674	27 421

Table 30 – Sex per incidence year

Sex	2015	2016	2017	2018	2019	2020	Total
Male	2 940 (65.8%)	2 829 (64.1%)	2 872 (63.0%)	2 915 (62.2%)	2 803 (60.6%)	2 850 (61.0%)	17 209 (62.8%)
Female	1 527 (34.2%)	1 582 (35.9%)	1 687 (37.0%)	1 771 (37.8%)	1 821 (39.4%)	1 824 (39.0%)	10 212 (37.2%)
ALL (100%)	4 467	4 411	4 559	4 686	4 624	4 674	27 421

The number of patients having more than one invasive lung cancer diagnosed during 2015-2020 was 1.3%, the year of incidence presented in Table 31 being the year of diagnosis of the first tumour. Globally, 3.7% of

the patients were diagnosed with another tumour than lung cancer after the diagnosis of the lung cancer. Note that the patients having another tumour than lung cancer were not retained in the selection.

Table 31 – Presence of different lung tumours per incidence year

Number of lung tumours	2015	2016	2017	2018	2019	2020	Total
1	4 406 (98.6%)	4 365 (99.0%)	4 499 (98.7%)	4 616 (98.5%)	4 556 (98.5%)	4 602 (98.5%)	27 044 (98.6%)
2 or more	61 (1.3%)	46 (1.0%)	60 (1.3%)	70 (1.5%)	68 (1.4%)	72 (1.5%)	377 (1.3%)
ALL (100%)	4 467	4 411	4 559	4 686	4 624	4 674	27 421

**Table 32 – Presence of tumours other than lung cancer diagnosed after the lung cancer, per incidence year**

Other cancer (after lung cancer incidence date)	2015	2016	2017	2018	2019	2020	Total
No	4 299 (96.2%)	4 229 (95.9%)	4 363 (95.7%)	4 515 (96.4%)	4 456 (96.4%)	4 547 (97.3%)	26 409 (96.3%)
Yes	168 (3.8%)	182 (4.1%)	196 (4.3%)	171 (3.6%)	168 (3.6%)	127 (2.7%)	1 012 (3.7%)
ALL (100%)	4 467	4 411	4 559	4 686	4 624	4 674	27 421

5.3.2. Health care costs

5.3.2.1. Percentages of patients receiving health care per cost item

Table 33 presents, for each cost item, the percentage of patients who received (have been billed) health care services (at least one included in the

category) in each stage and histological type. The same results are given for the most recent incidence year (2020) in Table 34. Results from this second table must be interpreted with caution for several reasons. First, the IMA – AIM data were only available until mid-2022 at the time of data extraction. Second, the exhaustiveness of the data cannot be guaranteed from 2021 due to the legal maximum billing delay of two years. And finally, the number of patients are limited in some groups diagnosed in 2020.

Table 33 – Percentage of patients per cost item, histological type and stage (all incidence years)

Percentage of patients per histological type and stage (all incidence years)							
ALL incidence years		N patients	Diagnosis and staging	Surgery	Percentage patients with		
Type	Stage				Radiotherapy	Systemic therapy	Palliative Care
NSCLC+Others	I	4735	99.8%	70.8%	35.2%	22.0%	11.6%
	II	1893	99.6%	71.1%	44.6%	70.7%	23.9%
	III	4567	99.8%	19.6%	67.9%	85.5%	36.5%
	IV	10816	99.6%	4.2%	53.7%	77.9%	51.3%
	X	999	99.4%	7.9%	41.3%	48.3%	32.5%
	All NSCLC+Others	23010	99.7%	26.6%	51.4%	66.0%	37.1%



SCLC	I	107	100%	47.7%	61.7%	79.4%	36.4%
	II	118	100%	24.6%	75.4%	94.1%	39.8%
	III	1016	>99.5%	3.1%	81.0%	93.1%	46.9%
	IV	2894	99.7%	0.2%	52.2%	86.4%	60.5%
	X	276	>98.2%	<1.8%	48.2%	68.5%	43.8%
	All SCLC	4411	99.7%	2.7%	59.5%	86.9%	55.2%
TOTAL		27421	99.7%	22.8%	52.7%	69.4%	40.0%

Small cells have been masked for patient sensitive data privacy reason.

Table 34 – Percentage of patients per cost item, histological type and stage (incidence year 2020)

Incidence year=2020		N patients	Percentage patients with				
Type	Stage		Diagnostics	Surgery	Radiotherapy	Systemic therapy	Palliative Care
NSCLC+Others	I	843	>99.4%	65.4%	33.5%	16.3%	5.3%
	II	300	100%	71.3%	35.7%	64.0%	15.0%
	III	738	>99.3%	22.1%	65.7%	85.4%	25.3%
	IV	1919	>99.7%	3.6%	50.2%	80.3%	44.6%
	X	116	100%	8.6%	37.1%	44.8%	31.9%
	All NSCLC+Others	3916	99.8%	25.7%	48.0%	65.1%	29.9%
SCLC	I	16	100%	37.5%	81.3%	87.5%	50.0%
	II	18	100%	27.8%	61.1%	88.9%	27.8%
	III	160	100%	<3.1%	81.3%	93.1%	36.3%
	IV	538	>99.1%	<0.9%	48.5%	86.8%	58.7%
	X	26	100%	.	26.9%	53.8%	19.2%
	All SCLC	758	>99.3%	1.8%	55.7%	87.1%	51.7%
Total		4674	99.8%	21.8%	49.3%	68.7%	33.4%

Small cells have been masked for patient sensitive data privacy reason.



5.3.2.2. Health care costs per cost item

Considering that IMA – AIM data were available one year before each incidence date until mid-2022, they are exhaustive only in the case of the diagnostic and staging costs (Table 35). For the average costs of the other costs items (Table 37, Table 38, Table 40, Table 41 and Table 42), the five-year follow-up is only guaranteed for the first incidence years (2015, 2016 and 2017). The follow-up for the costs of patients diagnosed in 2018, 2019 and 2020 are respectively between 3.5 and 4.5, 2.5 and 3.5 years, and 1.5 and 2.5 years, depending on the exact date of incidence in the year.

Moreover, due to the the legal maximum delay of two years to reimburse a health care service, costs incurred from the second half of 2020 might not have been reimbursed, recorded in IMA – AIM data and transferred to BCR at the time of data extraction.

In this descriptive section, the average costs are simple arithmetic means, calculated on patients with costs, instead of the half-cycle method applied for the inputs of the economic evaluation (see 5.2.3.3).

Table 35 – Diagnostic and staging costs, per histological type, stage and year of incidence

		Mean diagnostic and staging costs (€)						
		Incidence year						
		2015	2016	2017	2018	2019	2020	Total
Type	Stage							
NSCLC+Others	I	2172.9	2117.1	2075.5	2086.9	1892.5	1869.0	2028.4
	II	2503.5	2494.0	2415.3	2357.5	2214.7	2194.5	2365.5
	III	2246.1	2144.3	2180.4	2187.0	2248.0	2197.8	2200.7
	IV	2006.5	2002.2	1997.6	1961.4	1987.1	1956.4	1984.6
	X	1786.3	1700.9	1735.9	1736.5	1552.2	1661.1	1714.4
SCLC	I	2076.1	1978.5	2182.9	2057.8	2146.9	2224.5	2120.4
	II	2163.1	1976.7	1845.1	1980.6	2141.1	2153.0	2015.5
	III	1892.4	1868.9	1817.3	1917.9	1855.1	1897.3	1875.2
	IV	1581.3	1645.9	1624.3	1627.3	1650.2	1663.8	1633.3
	X	1606.8	1515.2	1376.1	1350.0	1381.1	1493.5	1482.2
ALL		2044.2	2015.6	2009.6	2001.5	1976.6	1950.2	1999.1



Table 36 presents the number and percentage of patients who underwent a certain type of examination in the three months before or after the incidence date of their lung tumours.

Table 36 – Number of patients per diagnostic and staging cost category, per histological type

Category	Subcategory	Type		SCLC		TOTAL	
		NSCLC+Others					
		N	%	N	%	N	%
Biopsy	Biopsy	6884	29.9%	723	16.4%	7607	27.7%
Endoscopy	Bronchoscopy	15027	65.3%	3088	70.0%	18115	66.1%
	EBUS	6129	26.6%	1072	24.3%	7201	26.3%
	EUS	926	4.0%	208	4.7%	1134	4.1%
	Gastrointestinal endoscopy	3573	15.5%	747	16.9%	4320	15.8%
	Mediastinoscopy	2525	11.0%	172	3.9%	2697	9.8%
	Tracheoscopy	2089	9.1%	409	9.3%	2498	9.1%
Cyto-histopathology	Cytology	17386	75.6%	3513	79.6%	20899	76.2%
	Histology	20401	88.7%	3881	88.0%	24282	88.6%
	Immunohistochemistry	8729	37.9%	150	3.4%	8879	32.4%
	Molecular biology	11575	50.3%	145	3.3%	11720	42.7%
Medical Imaging	Bone Scintigraphy-SPECT	4210	18.3%	1073	24.3%	5283	19.3%
	CT body	22436	97.5%	4335	98.3%	26771	97.6%
	CT brain	11763	51.1%	2748	62.3%	14511	52.9%
	CT neck	1587	6.9%	281	6.4%	1868	6.8%
	MRI thorax and abdomen	1194	5.2%	198	4.5%	1392	5.1%
	MRI brain	10154	44.1%	2043	46.3%	12197	44.5%
	PET-CT	17685	76.9%	2680	60.8%	20365	74.3%
	RX thorax	20651	89.7%	3900	88.4%	24551	89.5%
	Scintigraphy-SPECT	6729	29.2%	1419	32.2%	8148	29.7%



Lung	Lung function testing	17843	77.5%	2991	67.8%	20834	76.0%
MDT	Multidisciplinary team meeting	20816	90.5%	4000	90.7%	24816	90.5%
Staging	Staging (exploratory thoracotomy)	673	2.9%	56	1.3%	729	2.7%
Total (100%)		23010	100%	4411	100%	27421	100%

Small cells have been masked for patient sensitive data privacy reason.

The surgery costs, which are presented in Table 37, includes all the costs of the hospitalisation during which the surgery was performed, except if the costs are already included in the other cost items (to avoid double counting).

Table 37 – Surgery costs

		Mean surgical hospitalisation costs (€)						
		Incidence year						
		2015	2016	2017	2018	2019	2020	Total
Type	Stage							
NSCLC+Others	I	11994.7	11404.0	11743.8	11518.3	12044.9	11387.2	11684.4
	II	13114.9	12210.2	12153.7	12392.2	12365.3	12123.6	12406.4
	III	11303.8	12470.2	13132.3	12486.9	13767.0	12668.3	12677.3
	IV	12174.6	10979.8	13056.5	14363.9	13920.3	12492.0	12704.5
	X	10701.1	10507.1	18700.4	11177.6	13162.2	11509.6	12249.4
SCLC	I	13806.0	11205.9	13480.2	16482.4	15855.3	25718.8	15704.0
	II	20693.2	20562.2	12290.2	11350.7	15047.0	8404.6	13347.9
	III	11848.5	9661.1	7926.5	17705.7	12732.9	10058.0	12772.1
	IV	15923.7	.	8589.7	.	13972.4	5063.5	10950.3
	X	.	.	.	7754.9	.	.	7754.9
ALL		12232.2	11649.1	12209.5	12115.2	12551.5	11882.8	12108.4

** no information reported since there were no patients with reported relevant costs.*

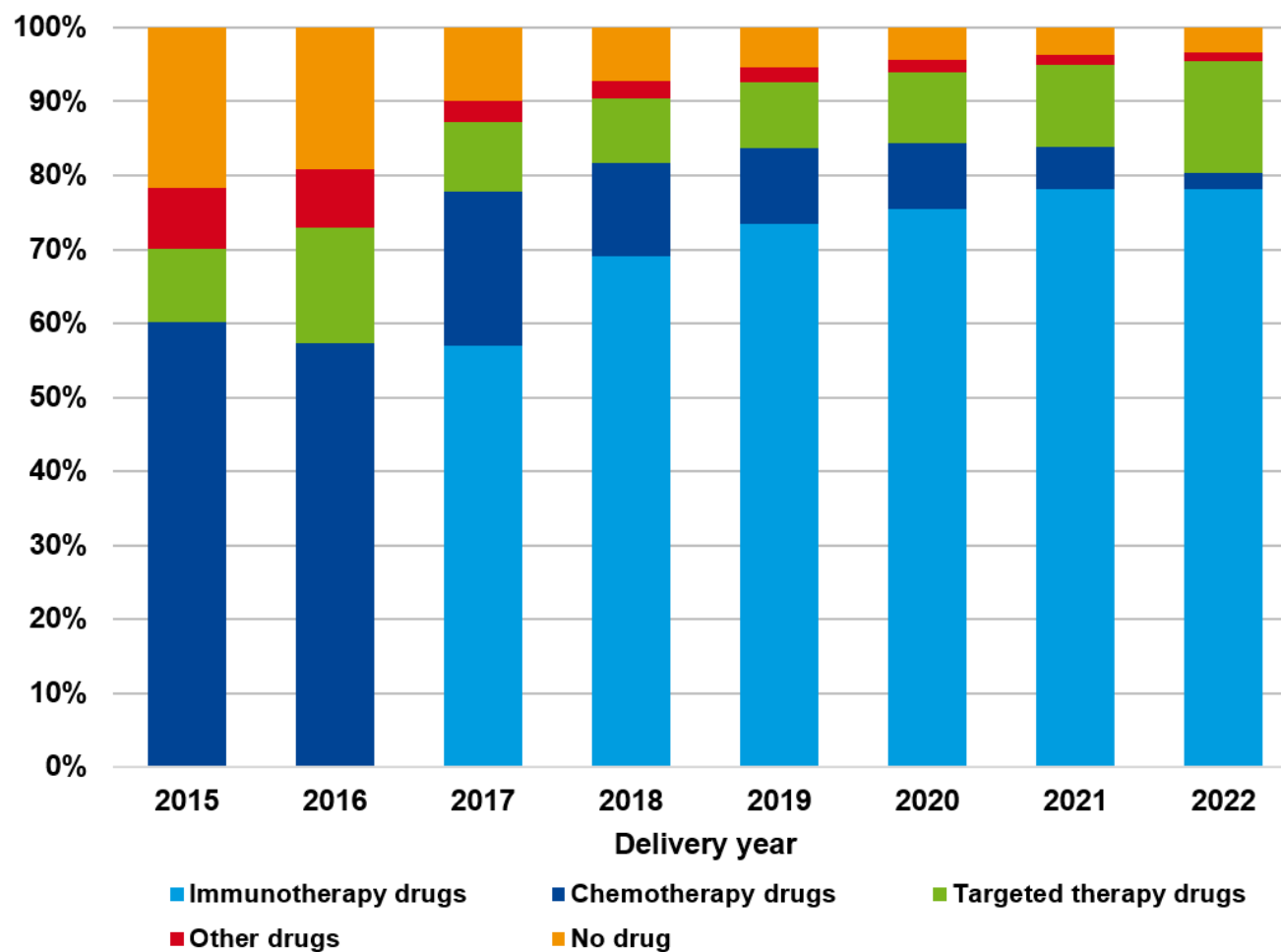


As explained in the methodology in section 5.2.3.3, costs presented in Table 38 include the costs incurred the same day of the delivery of the systemic therapy, i.e., all costs when the delivery is done in hospital setting, except a few exceptions (see section 5.2.3.3) and all pharmaceutical costs when it is done in the community setting). The cost drivers behind the systemic therapy costs were mostly the pharmaceutical products delivered as a systemic therapy (especially immunotherapy). Over the whole period, the shares of the bill were 70% for the immunotherapy products, 12% for the

chemotherapy products, 10% for the targeted therapy products, 6% for the non pharmaceutical costs and 2% for the other drugs. These results were not constant over time: not surprisingly the immunotherapy products represented 0.2% of the costs incurred when it was first reimbursed in 2016 but 78% in 2022. Conversely, the chemotherapy products accounting for 60% of the cost item in 2015 dropped to 2% in 2022 (Figure 16). Note that the total costs increased over time as presented in Table 38.

Table 38 – Systemic therapy costs

		Mean systemic therapy costs (€)						
		Incidence year						
		2015	2016	2017	2018	2019	2020	Total
Type	Stage							
NSCLC+Others	I	33467.1	39664.3	50348.9	52519.0	34930.9	34489.9	41506.4
	II	23336.3	36062.3	41008.8	38734.8	36889.8	22683.9	33201.7
	III	28070.2	46736.1	51810.2	46613.6	64863.6	56953.1	49359.0
	IV	32597.6	46367.3	70082.7	84591.9	98080.9	88377.2	71353.5
	X	27659.2	42688.7	41051.9	68588.3	73214.7	55578.3	44546.6
SCLC	I	5574.0	4695.1	8845.5	9649.2	13803.5	21823.9	11410.1
	II	3374.3	6956.3	14859.4	25282.1	34787.5	18343.6	18727.1
	III	7056.3	10132.1	9434.2	13966.5	22964.6	21187.4	14153.5
	IV	5786.2	6662.1	6930.8	11431.3	39078.3	49545.3	21023.9
	X	5156.5	5768.7	5942.2	11857.0	27645.4	19160.5	8717.2
ALL		25354.7	37585.3	50153.0	56502.5	70440.4	65747.0	51178.6

**Figure 16 – Systemic therapy costs components, per delivery year**

Source: BCR – IMA – AIM data.

Note: The drug expenditures are gross expenditures not taking into account the impact of confidential discounts and taxes.

**Table 39 – Number of patients per ATC code**

The following table presents the percentage of patients who received a particular ATC code (at least one billing) in the five years after diagnosis (including the 7 days margin before the incidence date).

Type of therapy	ATC code	Histological type					
		NSCLC+Others		SCLC		Total	
		N	%	N	%	N	%
Chemotherapy	L01AA01_Cyclophosphamide	73	0.3%	374	8.5%	447	1.6%
	L01AA02_Chlorambucil	<5	<0.1%	<5	≤0.1%	<10	<0.1%
	L01AA03_Melphalan	8	<0.1%	.		8	<0.1%
	L01AA06_Ifosfamide	53	0.2%	21	0.5%	74	0.3%
	L01AA09_Bendamustine	<5	<0.1%	.		<5	<0.1%
	L01AC01_Thiotepa	<5	<0.1%	.		<5	<0.1%
	L01AD01_Carmustine	<5	<0.1%	.		<5	<0.1%
	L01AD02_Lomustine	<5	<0.1%	.		<5	<0.1%
	L01AX03_Temozolomide	28	0.1%	43	1.0%	71	0.3%
	L01AX04_Dacarbazine	<5	<0.1%	<5	≤0.1%	<10	<0.1%
	L01BA04_Pemetrexed	7018	30.5%	26	0.6%	7044	25.7%
	L01BB02_Mercaptopurine	<5	<0.1%	.		<5	<0.1%
	L01BB05_Fludarabine	<5	<0.1%	.		<5	<0.1%
	L01BC01_Cytarabine	12	0.1%	<5	≤0.1%	<17	≤0.1%
	L01BC02_Fluorouracil	181	0.8%	43	1.0%	224	0.8%
	L01BC05_Gemcitabine	2993	13.0%	22	0.5%	3015	11.0%
	L01BC06_Capecitabine	22	0.1%	<5	≤0.1%	<27	≤0.1%
	L01BC07_Azacitidine	<5	<0.1%	<5	≤0.1%	<10	<0.1%



Type of therapy	ATC code	Histological type					Total	
		NSCLC+Others		SCLC		N		%
		N	%	N	%			
	L01BC08_Decitabine	.		<5	≤0.1%	<5	<0.1%	
	L01BC59_Trifluridine, Combinations	<5	<0.1%	.		<5	<0.1%	
	L01CA01_Vinblastine	6	<0.1%	<5	≤0.1%	<11	<0.1%	
	L01CA02_Vincristine	34	0.1%	339	7.7%	373	1.4%	
	L01CA03_Vindesine	.		<5	≤0.1%	<5	<0.1%	
	L01CA04_Vinorelbine	3248	14.1%	17	0.4%	3265	11.9%	
	L01CB01_Etoposide	1456	6.3%	3791	85.9%	5247	19.1%	
	L01CD01_Paclitaxel	966	4.2%	80	1.8%	1046	3.8%	
	L01CD02_Docetaxel	2424	10.5%	31	0.7%	2455	9.0%	
	L01CD04_Cabazitaxel	<5	<0.1%	.		<5	<0.1%	
	L01CE01_Topotecan	32	0.1%	906	20.5%	938	3.4%	
	L01CE02_Irinotecan	38	0.2%	28	0.6%	66	0.2%	
	L01CX01_Trabectedin	<5	<0.1%	<5	≤0.1%	<10	<0.1%	
	L01DA01_Dactinomycin	<5	<0.1%	.		<5	<0.1%	
	L01DB01_Doxorubicin	68	0.3%	312	7.1%	380	1.4%	
	L01DB02_Daunorubicin	<5	<0.1%	<5	≤0.1%	<10	<0.1%	
	L01DB03_Epirubicin	62	0.3%	89	2.0%	151	0.6%	
	L01DB07_Mitoxantrone	<5	<0.1%	<5	≤0.1%	<10	<0.1%	
	L01DC01_Bleomycin	24	0.1%	<5	≤0.1%	<29	≤0.1%	
	L01DC03_Mitomycin	60	0.3%	5	0.1%	65	0.2%	



Type of therapy	ATC code	Histological type					
		NSCLC+Others		SCLC		Total	
		N	%	N	%	N	%
	L01XA01_Cisplatin	9252	40.2%	1737	39.4%	10989	40.1%
	L01XA02_Carboplatin	6106	26.5%	2793	63.3%	8899	32.5%
	L01XA03_Oxaliplatin	73	0.3%	16	0.4%	89	0.3%
	L01XB01_Procarbazine	<5	<0.1%	.		<5	<0.1%
	L01XD04_Aminolevulinic Acid	35	0.2%	<5	≤0.1%	<40	≤0.1%
	L01XF01_Tretinoin	<5	<0.1%	.		<5	<0.1%
	L01XX05_Hydroxycarbamide	36	0.2%	<5	≤0.1%	<41	≤0.1%
	L01XX11_Estramustine	<5	<0.1%	.		<5	<0.1%
	L01XX23_Mitotane	<5	<0.1%	<5	≤0.1%	<10	<0.1%
	L01XX35_Anagrelide	<5	<0.1%	.		<5	<0.1%
	L01XX41_Eribulin	5	<0.1%	.		5	<0.1%
Immunotherapy	L01FF01_Nivolumab	2180	9.5%	33	0.7%	2213	8.1%
	L01FF02_Pembrolizumab	5302	23.0%	20	0.5%	5322	19.4%
	L01FF03_Durvalumab	606	2.6%	53	1.2%	659	2.4%
	L01FF04_Avelumab	<5	<0.1%	.		<5	<0.1%
	L01FF05_Atezolizumab	923	4.0%	767	17.4%	1690	6.2%
	L01FF06_Cemiplimab	<5	<0.1%	.		<5	<0.1%
	L01FX04_Ipilimumab	6	<0.1%	<5	≤0.1%	<11	<0.1%
Targeted therapy	L01EA01_Imatinib	<5	<0.1%	.		<5	<0.1%
	L01EA02_Dasatinib	<5	<0.1%	.		<5	<0.1%
	L01EA03_Nilotinib	<5	<0.1%	.		<5	<0.1%



Type of therapy	ATC code	Histological type					
		NSCLC+Others		SCLC		Total	
		N	%	N	%	N	%
	L01EB01_Gefitinib	338	1.5%	<5	≤0.1%	<343	≤1.3%
	L01EB02_Erlotinib	578	2.5%	<5	≤0.1%	<583	≤2.1%
	L01EB03_Afatinib	156	0.7%	<5	≤0.1%	<161	≤0.6%
	L01EB04_Osimertinib	437	1.9%	<5	≤0.1%	<442	≤1.6%
	L01EC01_Vemurafenib	<5	<0.1%	.		<5	<0.1%
	L01EC02_Dabrafenib	11	<0.1%	.		11	<0.1%
	L01ED01_Crizotinib	110	0.5%	.		110	0.4%
	L01ED02_Ceritinib	15	0.1%	.		15	0.1%
	L01ED03_Alectinib	184	0.8%	.		184	0.7%
	L01ED05_Lorlatinib	22	0.1%	.		22	0.1%
	L01EE01_Trametinib	10	<0.1%	.		10	<0.1%
	L01EF01_Palbociclib	8	<0.1%	<5	≤0.1%	<13	<0.1%
	L01EF02_Ribociclib	<5	<0.1%	.		<5	<0.1%
	L01EF03_Abemaciclib	<5	<0.1%	.		<5	<0.1%
	L01EG02_Everolimus	29	0.1%	5	0.1%	34	0.1%
	L01EJ01_Ruxolitinib	<5	<0.1%	.		<5	<0.1%
	L01EK01_Axitinib	<5	<0.1%	<5	≤0.1%	<10	<0.1%
	L01EL01_Ibrutinib	<5	<0.1%	.		<5	<0.1%
	L01EX01_Sunitinib	<5	<0.1%	<5	≤0.1%	<10	<0.1%
	L01EX02_Sorafenib	<5	<0.1%	.		<5	<0.1%
	L01EX03_Pazopanib	8	<0.1%	<5	≤0.1%	<13	<0.1%



Type of therapy	ATC code	Histological type					
		NSCLC+Others		SCLC		Total	
		N	%	N	%	N	%
	L01EX05_Regorafenib	<5	<0.1%	.		<5	<0.1%
	L01EX07_Cabozantinib	5	<0.1%	<5	≤0.1%	<10	<0.1%
	L01EX08_Lenvatinib	<5	<0.1%	.		<5	<0.1%
	L01EX09_Nintedanib	668	2.9%	5	0.1%	673	2.5%
	L01EX10_Midostaurin	<5	<0.1%	<5	≤0.1%	<10	<0.1%
	L01FA01_Rituximab	59	0.3%	6	0.1%	65	0.2%
	L01FC01_Daratumumab	5	<0.1%	.		5	<0.1%
	L01FD01_Trastuzumab	16	0.1%	<5	≤0.1%	<21	≤0.1%
	L01FD02_Pertuzumab	<5	<0.1%	.		<5	<0.1%
	L01FD03_Trastuzumab Emtansine	<5	<0.1%	.		<5	<0.1%
	L01FE01_Cetuximab	21	0.1%	<5	≤0.1%	<26	≤0.1%
	L01FE02_Panitumumab	<5	<0.1%	.		<5	<0.1%
	L01FG01_Bevacizumab	76	0.3%	.		76	0.3%
	L01FG02_Ramucirumab	9	<0.1%	.		9	<0.1%
	L01FX05_Brentuximab Vedotin	<5	<0.1%	.		<5	<0.1%
	L01FX10_Olaratumab	5	<0.1%	.		5	0.0%
	L01XG01_Bortezomib	7	<0.1%	.		7	<0.1%
	L01XG02_Carfilzomib	<5	<0.1%	<5	≤0.1%	<10	<0.1%
	L01XG03_Ixazomib	<5	<0.1%	.		<5	<0.1%
	L01XJ01_Vismodegib	<5	<0.1%	.		<5	<0.1%
	L01XX44_Aflibercept	<5	<0.1%	.		<5	<0.1%



Type of therapy	ATC code	Histological type					
		NSCLC+Others		SCLC		Total	
		N	%	N	%	N	%
		23010	100%	4411	100%	27421	100%

* no information reported since there were no patients with reported relevant costs.

Small cells have been masked for patient sensitive data privacy reason. Changes in ATC codes over time have been taken into account, the most recent ATC code is listed in the above table.

Average radiotherapy costs are presented per incidence year in Table 40. The stereotactic body radiation therapy (SBRT) is reimbursed since 1st of January 2020 only in Belgium. The costs pertaining to these techniques are shown per delivery year in Table 41.

Table 40 – Radiotherapy costs, per incidence year

		Mean Radiotherapy costs (€)						
		Incidence year						
		2015	2016	2017	2018	2019	2020	Total
Type	Stage							
NSCLC+Others	I	4829.6	5271.0	5415.7	4826.3	5054.1	4838.3	5035.9
	II	4733.5	5490.2	5503.4	5648.4	4894.8	5086.5	5230.3
	III	5583.7	5501.8	5307.9	5655.9	5326.2	5242.3	5440.1
	IV	4714.0	4765.1	5230.4	5306.0	5092.2	5129.9	5038.2
	X	4479.5	4302.8	4271.6	4947.3	4634.1	5266.9	4560.9



SCLC	I	5046.6	4636.9	6123.3	5825.7	5136.5	7392.2	5765.4
	II	6289.1	5985.2	7593.6	6797.8	6786.2	5871.8	6714.4
	III	6927.6	6620.0	6932.0	7298.2	6693.2	6211.3	6795.8
	IV	4243.3	4584.7	4773.9	4630.9	4545.8	4682.3	4578.1
	X	6412.8	5486.0	5015.9	4965.3	5181.0	5385.1	5658.1
ALL		5005.8	5090.3	5337.1	5402.6	5176.5	5145.8	5193.1

Table 41 – Stereotactic body radiation therapy (SBRT) costs

		SBRT delivery year							
		2020		2021		2022		Total	
		N	Mean Costs (€)	N	Mean Costs (€)	N	Mean Costs (€)	N	Mean Costs (€)
Type	Stage								
NSCLC+Others	I	203	2887.0	144	2983.1	26	2824.1	373	2919.7
	II	50	2943.2	47	3101.9	14	3371.7	111	3064.4
	III	84	3196.4	91	3118.4	26	2925.0	201	3126.0
	IV	268	3227.2	202	3286.5	35	3146.9	505	3245.3
	X	14	2950.5	12	3254.3	<5	3933.6	<31	3150.9
SCLC	I	<5	1936.3	<5	2603.4	.	*	<10	2158.7
	II	<5	2581.7	<5	2603.4	<5	2622.4	<15	2597.3
	III	12	3227.2	15	2950.5	<5	2622.4	<32	3028.4
	IV	26	2978.9	23	2943.0	17	2930.9	66	2954.0
	X	<5	2581.7	<5	2603.4	.	.	<10	2598.0
ALL		664	3071.6	540	3128.9	124	3024.2	1328	3090.5

* no information reported since there were no patients with reported relevant costs.
Small cells have been masked for patient sensitive data privacy reason.



Table 42 – Palliative care costs

		Mean palliative care costs (€)						
		Incidence year						
		2015	2016	2017	2018	2019	2020	Total
Type	Stage							
NSCLC+Others	I	6476.8	8106.0	7774.6	6464.2	6229.2	3858.4	6764.3
	II	4409.1	3785.8	6609.5	6173.1	6382.8	4144.7	5159.5
	III	3877.9	5041.0	4545.7	4525.3	3729.2	3941.8	4324.1
	IV	3296.4	3684.2	3561.5	4006.9	4093.2	3862.9	3742.2
	X	3693.6	4467.5	4714.6	3501.4	1662.6	3448.8	3883.7
SCLC	I	4792.2	3542.4	2812.1	5087.7	6763.5	4263.4	4697.2
	II	7326.8	4279.3	2088.1	3208.6	14860.6	4272.8	5327.7
	III	2219.5	2674.2	5882.7	4072.1	5442.1	4346.9	4133.0
	IV	3468.8	3268.9	3692.5	3593.6	4210.4	3673.4	3670.2
	X	4075.5	5772.3	1482.5	4029.1	2540.8	4292.9	4112.5
ALL		3654.0	4100.8	4211.6	4250.1	4314.9	3854.9	4064.1



Key Points

Patients characteristics

Patients selected on the BCR - IMA – AIM database (first lung cancer incidence between 50 and 74 years in the period 2015-2020, neither stage 0 nor in situ tumour, patient WHO status performance different from 4 with absence of other cancer) presented the following characteristics:

- Stage VI represented half the cases over the period 2015-2020, followed by stage III (20%). The undetermined stage X decreased from 7.5% until 3% in 2020. Small cells lung cancer concerned 16% of the patients. Another cancer was diagnosed after their lung cancer incidence in about 4% of the patients.
- Most patients were male (63%) and the most frequent age categories were 65-69 years (28%), 70-74 years (26%) and 60-64 years (23%).
- Applying the Kaplan-Meier method, almost 60% of the patients survived one year after their lung cancer diagnostic. A quarter of them were still alive after 5 years. The survival is lower in patients diagnosed with SCLC lung cancer (about 9% versus 30% in NSCLC patients at 5 years). As the mortality increased with the stage, the 5-year survival rate of patients with stage I non SCLC was 68% versus 3% for stage IV SCLC patients.

Health care costs

The present section presented the costs per cost item, calculated on patients who had received the cost item health care services.

- Almost all patients had at least one diagnostic code billed in the period spanning from 3 months before to 3 months after the date of lung cancer incidence. The average cost for diagnosis and staging services amounted to €2000, decreasing slightly with the incidence year. The highest means were found in patients with non SCLC, stage II and SCLC, stage I; the lowest in stage X whatever the

histological type. A multidisciplinary team meeting was registered in 90.5% of the cases.

- About 22% of the patients underwent a surgical intervention. The total hospitalisation costs for these surgeries was estimated around €12 000 and was more or less stable, whatever the incidence year.
- Systemic therapy costs, measured as all costs incurred on the day of pharmaceuticals delivery, reached in average €51 200. About 70% of the patients benefited from this therapy. The mean costs were higher in patients with stage IV and in patients with another histological type than SCLC. They increase with the incidence year, mainly due to the growing share of the immunotherapy pharmaceuticals over time.
- On average, radiotherapy, which concerned half of the patients, was estimated at €5200 per patient, including primary as well as palliative radiotherapy. Stereotactic body radiation therapy is reimbursed since the first of January 2020.
- The average palliative care costs, delivered to 40% of the patients, amounted to €4100, slightly increasing with the incidence year (except 2020 for which the follow-up was shorter than the other years).



6. ECONOMIC EVALUATION FOR BELGIUM

6.1. Methodology

In the economic evaluation, the cost-effectiveness of LDCT screening in an adult high-risk population, compared to no screening is evaluated. Based on the evidence presented in the clinical part of this report, we chose to determine the cost-effectiveness based on the results of the NELSON trial. This landmark trial is the second largest trial to demonstrate a reduction in lung cancer mortality, and implemented volumetric nodule management, resulting in higher specificity compared to the NLST. Furthermore, the introduction of a third "indeterminate" screening test aimed to minimize false positive CT screening results. In this Dutch-Belgian RCT, approximately six percent of the participants were Belgian.²²⁴

This RCT evidence is supplemented with further information from the literature (e.g., on QoL), Belgian survival data from lung cancer patients (all-cause mortality according to stage and histology) and Belgian cost information.

6.1.1. Patient population

The inclusion criteria of the NELSON trial were as follows:^{10, 225}

- People aged between 50 and 75 years AND
- Smoked at least 10 cigarettes a day for at least 30 years
- OR at least 15 cigarettes a day for at least 25 years
- OR former smokers who had such a smoking history and who had quit smoking less than 10 years ago.

People with self-reported moderate or bad health (first question of SF-36), inability to climb two flights of stairs, bodyweight of 140 kg or more, current or past renal cancer, melanoma, or breast cancer, lung cancer diagnosed

less than five years ago, or a chest CT examination less than one year ago, were excluded.²²⁴

Finally, in the NELSON trial, the included patients (n=15 822) had the following characteristics:²²⁴

- Male/female: 13 225/2597 (84% male)
- Current smoker: 55%
- Median age: 58.0 years (interquartile range (IQR): 54.0 – 62.0)
- Median pack years: 38.0 (IQR: 29.7 – 49.5)

6.1.2. Intervention and comparator

In the intervention arm, participants undergo LDCT screening at baseline, year 1, year 3, and year 5.5.¹⁰ For CT screening, "*low-dose 16-multidetector or, in later rounds, 64-multidetector CT systems were used to acquire isotropic volume data, without administration of contrast medium. Apart from local readings, all images were analyzed centrally at UMCG [University Medical Center Groningen] with the use of semiautomated software (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions). The analysis included the semiautomated segmentation of nodules and determination of the nodule volume.*"^{226*10}

In the comparator arm, participants receive no screening. The absence of a screening programme for lung cancer reflects the situation in Belgium.

6.1.3. Type of economic evaluation

Quality of life is of major importance to patients with cancer and can be influenced by both the disease as well as by the treatments. Therefore, a cost-utility analysis (CUA) is performed. Results of the cost-effectiveness analysis (CEA), in which the years of life are not adjusted for quality of life, are also presented. Both incremental costs (IC), incremental effects (IE) in life years gained and QALYs gained, and incremental cost-effectiveness ratios (ICER) will be presented separately in the results section.



6.1.4. Perspective

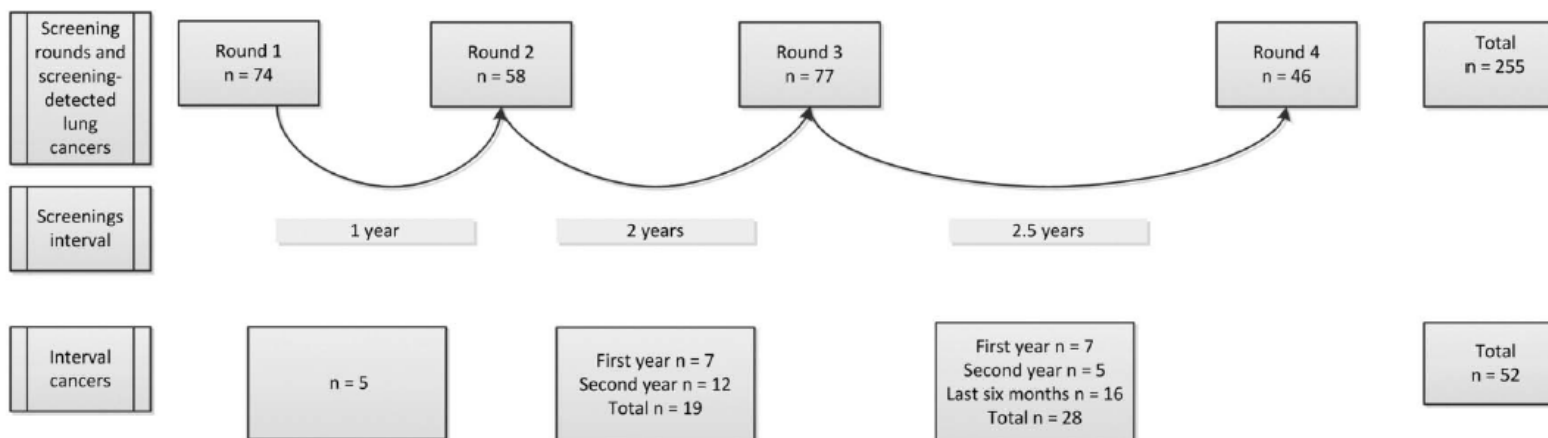
In accordance with the Belgian guidelines,²²⁷ the analysis is performed from the health care payer's perspective and includes direct health care costs. Following these guidelines, payments out of the government's health care budget as well as patients' co-payments, supplements excluded, are included. In a scenario analysis, patients' supplements are also included (Scenario 'supplements').

No extension to a societal perspective was modelled.

6.1.5. Time horizon and discount rate

In the NELSON trial, there are four screening rounds: at 0, 1, 3 and 5.5 years (see Figure 17). In the NELSON protocol, it is mentioned that "in 2018, the Mortality Advisory Board indicated that screening effectiveness may vary over time and suggested evaluating the appropriateness of the chosen time-point (10-years since randomization) for the endpoint evaluation.²²⁸... The NELSON-like scenario indicates that it is expected that the four CT-scans in NELSON would show its maximum effect at around 8-9 years of follow-up after baseline, and is expected to level off after 10 years since randomization."²²⁵

Figure 17 – Overview of the screening-detected lung cancers and interval cancers across the four screening rounds



Source: Figure 3 from Yousaf-Khan et al., Thorax, 2017²²⁹



The screening intervals varied in the NELSON trial study. The results show that the number of interval cancers is much higher at an interval of 2.5 years, which was an indication to experts that the duration of this screening interval was too long. A screening interval of one or two years is up for debate,²³⁰ and the ongoing 4-IN-THE-LUNG-RUN trial^v aims to answer questions concerning personalized strategies in recruitment and screening intervals (biennial versus annual in those with a negative baseline LDCT).²³¹ The separate reporting of interval cancers up to 5 years (instead of 5.5 years) allows us to reduce the interval of the 3rd round in the economic model to 2 years. In total, we consider all identified cancers up to 5 years in both the screening and no screening arm.

The cancers identified in the lung cancer screening and comparator group are linked to costs and effects. Initially, the analysis is performed over a time horizon of 10 years. Based on the Mortality Advisory Board, this period should be sufficient to capture most of the benefits of lung cancer screening. Furthermore, the results are extrapolated over a lifetime horizon to capture the full possible impact on relevant incremental costs and effects. The short time horizon of 10 years has the advantage of being less influenced by the uncertainty surrounding the extrapolation phase of the economic model. This time horizon is also used to validate the results of the model (see part 6.1.9). On the other hand, a longer time horizon has the advantage of taking longer term incremental impacts into account. Therefore, for all further analyses, results in combination with both the 10-year and lifetime time horizon scenarios will be presented.

According to the Belgian guidelines for economic evaluations,²²⁷ a yearly discount rate of 3% and 1.5% for costs and effects, respectively, is applied in the base case. Following the guidelines, 0%, 3% and 5% for both costs and effects is applied in scenario analyses (Scenario 'discount rate'). Given the monthly cycles in the model (see part 6.1.6), the yearly discount rates are transferred to monthly percentages (1.5%/year → 0.1241%/month; 3%/year → 0.2466%/month; 5%/year → 0.4074%/month).

6.1.6. Model structure

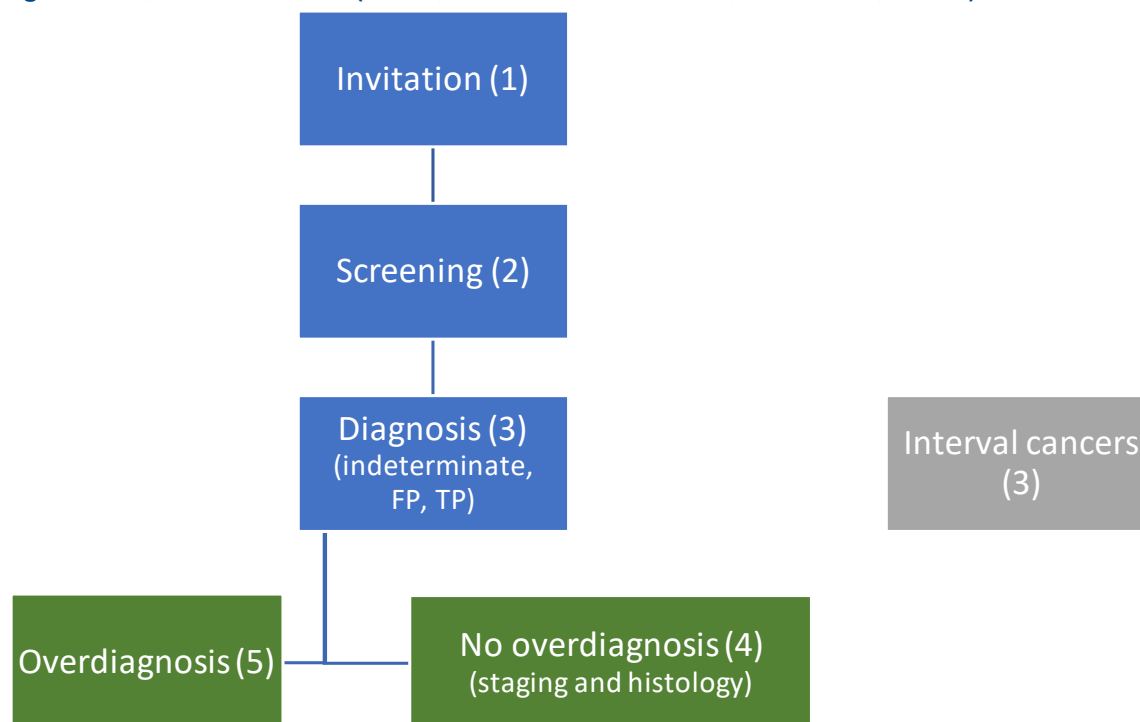
The model is a combination of a decision tree and a Markov model. In the first stage, costs for invitation, screening and diagnosis are modelled through a decision tree. Then, lung cancers in the intervention and comparator group are linked to costs and effects in a Markov model. It was decided to present the cost information based on the Belgian data analysis for the first three months after the lung cancer diagnosis per month (see Chapter 0). Therefore, the Markov model contains monthly cycles. A simplified representation of the model structure is provided in Figure 18.

^v The EU-funded 4-IN THE LUNG RUN trial (INdividually tailored INvitations, screening INtervals, and INtegrated co-morbidity reducing strategies in lung

cancer screening) is a multicenter implementation trial underway in five European countries. The planned study end date is December 2024.



Figure 18 – Model structure (combination of decision tree and Markov model)



Blue: information related to invitation, screening and diagnosis is modelled as a decision tree. Green: information related to detected cancers is modelled as a Markov model. Grey: Interval cancers are assumed to be the same across the intervention and comparator group (i.e., no incremental differences were modelled). For further information: (1) see part 6.1.7.1; (2) see part 6.1.7.2; (3) see part 6.1.7.3; (4) see part 6.1.7.4; (5) see part 6.1.7.5.



6.1.7. Input parameters

6.1.7.1. Invitation

An overview of the input variables related to the LCS invitation is presented in Table 43.

Table 43 – Overview of input variables (invitation to LCS in the NELSON trial)

Variable	Value	Uncertainty	Source
Invitation			
• First questionnaire	606 409 individuals	Fixed	NELSON trial ¹⁰
• First response	150 920 individuals	Beta (150 920; 455 489*) (24.9%)	NELSON trial ¹⁰
• Eligible and invited	30 959 individuals	Beta (30 959; 119 961) (20.5%)	NELSON trial ¹⁰
• Second response & inclusion in NELSON (i.e., participation screening as a percentage of eligible and invited persons)	15 822 individuals	Beta (15 822; 15 137) (51.1%) Scenario 'participation': • 30%: Beta (9288; 21 671) • 40%: Beta (12 384; 18 575) • 60%: Beta (18 575; 12 384) • 70%: Beta (21 671; 9288) • 80%: Beta (24 767; 6192) • 90%: Beta (27 863; 3096)	NELSON trial ¹⁰
Adjustment for not randomizing patients (i.e., NELSON versus real-world LCS)			
• Adjustment factor	50.03% (7915 / (7915 + 7907))	Fixed	NELSON trial ¹⁰
Costs related to the invitation			
Invitation per letter (1 st round)	€0.407 → €0.5137 per invitation No extra costs assumed (e.g., for GP visit)	Uniform (0.8; 1.2) Scenario 'invitation cost': • Exclusion of this cost	Flanders Department of Care ²³² and personal communication
Invitation 2 nd or 3 rd round	€0.393 per invitation	• Use of costs for Wallonia and Brussels: €0.65 for all three rounds.	
Communication result screening			
Variable costs screening results	communication		



Variable	Value	Uncertainty	Source
- Electronic communication GP - Negative result - Indeterminate or positive result	€0.18 → €0.209 per electronic result letter - No extra cost - GP visit: €25.68	- Uniform (0.8; 1.2) - Scenario 'communication cost': €1.2408 per result letter by post / - Fixed	Flanders Department of Care ²³² and personal communication
Other costs related to screening campaign			
Costs within lump sum subsidy (invitation and registration system screening results, diagnostic feedback)	€5 166 874 + €234 887 (distributed over 1 426 127 persons – €3.79 per invited person)	Uniform (0.8; 1.2) Scenario 'invitation cost': exclusion of these costs	Personal communication Flanders Department of Care
Costs added to the lump sum subsidy:		Uniform (0.8; 1.2)	
Evaluation screening program (periodic working group)	€36 750 per year for all screening programs (distributed over 1 426 127 persons – €0.03 per invited person)	Scenario 'invitation cost': exclusion of these costs	Personal communication Flanders Department of Care
Costs to reach the LCS target population		Uniform (0.8; 1.2)	
Awareness campaigns	€556 568 (distributed over 819 137 persons – €0.68 per invited person)	Scenario 'invitation cost': exclusion of these costs	Flanders Department of Care ²³²

GP: general practitioner; LCS: lung cancer screening.

* A beta distribution is determined by two parameters. The alpha parameter equals the number of events. The beta parameter equals the size of the sample minus the number of events (e.g., in this case 606 409 – 150 920 = 455 489).

In the NELSON trial, on the basis of population registries, 606 409 persons 50 to 74 years of age who lived in four selected regions in the Netherlands and Belgium were approached with a general questionnaire and brief information about the trial in 2003 (first recruitment) or 2005 (second recruitment). A total of 30 959 respondents of the 150 920 who returned questionnaires were eligible.¹⁰ In the trial, these persons received a second questionnaire, an information brochure about the NELSON trial and an informed consent form in which they were invited to participate.²²⁵ Written consent was provided by 15 822 persons (51.1%), which were randomized

in the trial: 7915 persons in the screening arm and 7907 persons in the control arm. Thirty patients died after providing informed consent, resulting in 15 792 formal participants.¹⁰

This information is used in our economic model and costs from the Belgian setting are linked to the patient flow observed in the NELSON trial. Furthermore, some corrections are included to reflect what would happen when LCS would be introduced outside of this RCT setting:



- In the model, costs are only taken into account for the first invitation of 606 409 persons aged 50-74 years. The costs linked to the second invitation, in which an information leaflet about the NELSON trial was provided and written informed consent was requested, are not included in the model. In reality, the information leaflet will probably be already provided in the first invitation. Furthermore, eligibility for LCS will probably be indicated directly through the initial (online) questionnaire (see cost information further in this part).
- In the NELSON trial, patients are randomised while in reality this is not the case. It would be incorrect to allocate the costs of the invitation only to the intervention arm of the RCT. These costs are distributed over all 15 822 participants in the NELSON trial by applying an adjustment factor. Since all further information in the model is applied to the 7915 participants in the LCS arm, this is done by multiplying all previous costs for the invitation by 50.03%.
- In the NELSON trial, 30 959 individuals were eligible and invited for participation in the trial. Ultimately, 15 822 (51.1%) people agreed to participate. We apply these figures in the base case. However, participation in an evidence-based screening programme may be higher than participation in an RCT. In a scenario analyses, we modify the participation rate of 51.1% in steps of 10% from 30% up to 90%, thus distributing all costs prior to participation over a smaller or larger group of participants (Scenario 'participation').

Cost information

Currently, no lung cancer screening is organised in Belgium. For costs associated with population screening, we rely on information obtained from the Agency of Care from the Flemish government (personal communication), supplemented with public information on the financing of population screening (https://zorg-en-gezondheid.be/sites/default/files/2023-07/Financiering_Preventie_Bevolkingsonderzoek_2023.pdf).²³²

An initial cost for population-based lung cancer screening involves identifying and inviting the target population. There is currently no consensus on the strategy to follow. Should a decision be made to introduce population-based lung cancer screening, implementation research will be needed to determine the most effective strategy to reach the target group. However, we prefer to include these costs to make an appropriate economic evaluation. A possible scenario was explained by external experts involved in the research on lung cancer screening in Belgium. The costs of this invitation scenario were included in the economic model in combination with the evidence on eligibility and participation from the NELSON trial.

As there is no reliable database with data on smoking behaviour, a general invitation letter and/or brochure with a general information would initially be sent to all inhabitants within the age range. Based on the Population Screening for Cervical and Breast Cancer, the cost for this invitation was initially assumed to be €0.407 per invitation.²³² Based on more up-to-date information from the Flanders Department of Care, a cost of €0.5137 was included in the base case. Through this invitation letter, (former) smokers would be asked to go to a website to fill out a short questionnaire to determine whether they meet the inclusion criteria. The following information would be requested: age, smoking status (former or current smoker), smoking intensity (cigarettes per day), duration of smoking and duration of quitting. As not everyone in the target group will be able to complete the questionnaire via the website, the option of doing so via a trusted person, such as the GP or pharmacist, would be retained. In a conservative estimation of the costs, we assume that this is associated with a doctor or pharmacist visit that may have already taken place for other reasons. Therefore, we do not include additional costs for help of this trusted person. This potentially represents an underestimation of the actual incremental costs. Potentially additional costs, e.g., for sending a reminder letter, are also not taken into account, leading to a conservative estimate of the invitation costs.

Based on the information entered on the website, it is indicated whether the participant is eligible for screening. If this is the case, an appointment for an LDCT screening is made (see part 6.1.7.2)



The invitation for the 2nd or 3rd screening round would go through the registration and invitation system where a letter and/or email is sent to the participants listed in the system. In the baseline scenario, we assume that both a letter and e-mail are sent. In Population Screening Colorectal Cancer, there was a lower cost for a reminder letter of €0.393 per reminder. For the invitation to a 2nd or 3rd round, we charge this slightly lower cost.

In a scenario analysis, the invitation costs for the three rounds are excluded to see the impact of not taking into account this cost (Scenario 'invitation cost'). In another scenario, a higher cost of €0.65 per invitation letter for every round is included based on information received from BruPrev (organisation responsible for the organisation of cancer screening in Brussels) and CCRef (organisation responsible for the organisation of cancer screening in Wallonia).

A population screening goes beyond identifying and inviting the target group and carrying out the screening. It also includes the following components: registration and communication of screening results, diagnostic feedback to the Belgian Cancer Registry (BCR), quality control, evaluation of the screening programme, awareness campaigns, etc. We include costs for several of these activities based on the experience in Flanders with population screening.

1. Registration screening results:

- CvKO^w has developed a database/invitation system to automate the invitation and follow-up of screening, Heracles. The maintenance cost of this registration and invitation system Heracles is included in CvKO's lump-sum subsidy (see below). Over the years, CvKO has spent about €470 000 on this every year. But when a new population study is launched, an investment cost will have to be provided to extend the system to the new target group.

^w The Centre for Cancer Screening (Centrum voor Kankeropsporing – CvKO) is the centre of expertise in Flanders for population screening for cancer. It is

- In our base case, we take into account the lump-sum and variable subsidy (see below). The initial one-off investment cost to extend the system to lung cancer screening is not included. In that respect, a favorable calculation is made in which the initial costs for lung cancer screening are underestimated.

2. Communication of screening results:

- Screening results must be communicated to the GP. The costs from the population screening for colorectal cancer are: €0.556 per result letter the GP receives by mail or €0.18 per result letter the GP receives electronically. In the breast cancer population study, this was €0.726 and €0.18, respectively. Based on more up-to-date information from the Flanders Department of Care, the cost of €0.18 was finally updated to €0.209 (personal communication). In our model, we take the cost of €0.209 into account for all persons participating in the screening and apply a scenario with a cost of €1.2408 based on information received from CCRef (Scenario 'communication cost').²³²
- If the result of the screening test is negative, no further steps are taken. In the model, no further costs are taken into account.
- In case of an indeterminate or positive screening result, we assume that the screening participant will be invited to visit the GP to explain the result and further steps. In this case, a doctor's visit will be charged. We include a GP consultation in the model (Nomenclature 101032 - 'Consultation in the consulting room by a GP': €25.68). Note that it is also possible that the participant is informed by telephone and invited for a second screening examination or to start the diagnostic process, respectively (not included in the model).

3. Diagnostic feedback:

responsible for the implementation and coordination of these population screening programmes organised by the Flemish government (www.cvko.vlaanderen).



- The BCR collects data on all new cancer diagnoses in Belgium and their follow-up. In addition, the BCR also collects all anatomopathological test results in the context of early detection of certain cancers (cervical, breast and colorectal cancer).²³² The data from these registries are relevant for the efficient organisation, monitoring and evaluation of the three population-based cancer screening programmes.²³²
 - BCR receives an annual subsidy for the three population surveys. In 2023, this amounted to €234 887. This cost is added to the lump-sum subsidy (see below).
4. Quality control of execution
- Mammography units (radiology services) must be recognised by the Flemish government to perform screening mammograms. This involves a personnel cost at the administration. There will also be a cost for quality control for lung cancer screening. This falls outside the lump-sum costs charged in the model. Thus, there is a conservative underestimation of costs.
5. Evaluation of screening programme (periodic working group)
- Population screening by the Flemish government is continuously monitored and evaluated by, among others, multidisciplinary working groups. There is one specific working group per population screening and there are also two general working groups. The expense allowance for the experts in these working groups averages €120 per expert per meeting. Annually, there are about 3-4 meetings where an average of 15-20 members attend. This would amount to an annual cost of about €36 750. This cost is not included in the lump-sum subsidy. We add this cost to the lump-sum subsidy and allocate these costs to the lung cancer screening programme via a distribution key (see below).
6. Awareness campaigns
- To inform the target audience, it is also necessary to purchase media space. As an example, for the media campaign around the expansion of the population screening on congenital diseases, a public contract worth €356 568 was issued for the purchase of media space (TV spot and social media).²³² A lump sum of €200 000 was also provided for a new campaign, selecting media channels that allow for a more creative and impactful approach, also targeting hard-to-reach audiences (e.g., bread bags, shopping carts, etc.). The aim was to reach vulnerable people and people of low socioeconomic status in the specific places where they are, with messages that can generate attention to the Cancer Screening Programme.²³² To reach the target group of (former) smokers who often belong to a lower socioeconomic class, it is possible that additional efforts will have to be made.
 - These costs are not included in the lump-sum or variable subsidies. The cost of the two campaigns mentioned is charged in case an awareness campaign for LCS should be set up. In a scenario analysis, these costs are ignored (Scenario 'invitation cost').
7. Supplementary awareness campaign for smoking cessation
- If an LCS intervention were to be initiated, it would usually be accompanied by a smoking cessation intervention. The focus of costs in the economic model is on LCS-specific costs. These costs, as well as the potential consequences of smoking cessation, are conservatively excluded.
- The Flanders Department of Care pays an annual subsidy of the CvKO. The total annual cost for the three population-based cancer screenings (breast, colon, cervix) in 2023 was: (personal communication with Flanders Department of Care)
- Lump sum subsidy CvKO: €5 166 874
 - Variable subsidy CvKO: €3 272 863
- The costs linked to the variable subsidy (invitations, notification of results to doctors and participants, etc.) are already included directly in the economic model. The costs linked to the lump-sum subsidy, based on current screening programmes, are allocated to the various target groups via a distribution key. Also the cost of the periodic working groups of €36 750 are included using this distribution key.



Since participation can be very different by population screening type, we prefer to use the number of invited persons as the distribution key. We extract this information from the annual report of the CvKO (2022).²³³ The information is presented in Table 44. In 2022, about 1.43 million people were invited to participate in population screening for breast, colorectal or cervical cancer. If we divide the lump-sum subsidy of about €5.2 million, the annual

BCR subsidy for the three population surveys (see above) and the costs of the periodic working groups among these invited people, we obtain a cost of about €3.81^x per invited person.

Table 44 – Population screening in Flanders (number of invited persons)

Population screening	Breast cancer		Colorectal cancer		Cervical cancer		Total
Target population	Women 50-69 years		50-74 years		Women 25-64 years		
Screening interval	Biannual		Biannual		Three-yearly		
Year	2021	2022	2021	2022	2021	2022	2022
Full target group	889 876	892 889	2 128 798	2 138 119	1 726 412	1 730 186	4 761 194
Excluded persons**	282 143	NA	880 479	NA	797 548	NA	NA
Allowed target group**	607 733	NA	1 248 319	NA	928 864	NA	NA
Target group to be invited**	441 817	NA	857 335	NA	216 383	NA	NA
Total number of invited persons	438 947	378 553	853 011	731 787	272 915	315 787	1 426 127
Participated	241 041	209 939	448 127	353 800	447 682	453 002	
Response rate	53,2%	54.1%*	52.5%	48.3%	28.8%*	15.3%*	
Coverage rate	64%	64.7%	64.3%	64.2%	63.7%*	64.5%*	

Remark: For breast cancer screening, it was mentioned that in 2021 a higher number of invitations was sent, essentially to catch up the remaining COVID-19 backlog from 2020. Therefore, results from 2022 might be more reliable. NA: not available.

* Non-final information ** We refer to the original year report for detailed information on the underlying reasons for exclusion (e.g., refusal to be invited, invited in previous calendar year without attendance, attendance outside screening before an invitation could be sent, person in which a specific cancer is already detected, etc.).

^x (€5 166 874 + €234 887 + €36 750) / 1 426 127 = €3.81



Finally, the costs for the awareness campaigns are allocated specifically to the potential target group for LCS. The population over which this cost is distributed is estimated as follows: On 1 January, the Belgian population aged 50-74 was 3 559 783. Separate media campaigns will be needed in Flanders versus Wallonia and Brussels, partly because of language and because the federated entities are responsible for organising cancer screening programmes. In 2022, the entire target group of 50-74-year-olds in Flanders consisted of about 2.1 million people (see Table 44). As the previous campaigns show, the total number of people invited is much lower than the full target group. We have no idea what the ratio would be for LCS if such a campaign were to run for several years. For breast, colorectal and cervical cancer this was 42.4%, 34.2% and 18.3%, respectively. Experts

noticed the cervical cancer screening is rather atypical since persons not participating in opportunistic screening are invited. If the unweighted average of the two other campaigns (38.3%) is applied to the target group of about 2.1 million, this would equate to 819 137 people invited. If we allocate the annual cost of €556 568 for media campaigns to this group, this would equate to a cost of €0.68 per invited person. In the base case, we include this cost. In a scenario analysis, we exclude these costs.

6.1.7.2. Screening

An overview of the input variables related to the LDCT screening is presented in Table 45.

Table 45 – Overview of input variables LDCT screening (NELSON trial – men and women)

Variable	Value	Uncertainty	Source
Screening group	7915 → 7899*	Fixed	NELSON trial ¹⁰
LDCT (1st round)			
• Screening uptake (%)	7557/7899	Beta (7557; 342) (95.7%)	NELSON investigators
Findings:			NELSON investigators
• Negative	5921	/**	
• Indeterminate	1451/7557	Beta (1451; 6106) (19.2%)	
• Positive	185/7557	Beta (185; 7372) (2.4%)	
LDCT (2nd round)			
• Screening uptake (%)	7294/7756	Beta (7294; 462) (94.0%) Scenario 'adherence': 50%	NELSON investigators
Findings:			NELSON investigators
• Negative	6694	/**	
• Indeterminate	480/7294	Beta (480; 6814) (6.6%)	
• Positive	120/7294	Beta (120; 7174) (1.6%)	
LDCT (3rd round)			
• Screening uptake (%)	6921/7565	Beta (6921; 644) (91.5%) Scenario 'adherence': 50%	NELSON trial ¹⁰
Findings:			NELSON investigators
• Negative	6294	/**	
• Indeterminate	471/6921	Beta (471; 6450) (6.8%)	



Variable	Value	Uncertainty	Source
• Positive	156/6921	Beta (156; 6765) (2.3%)	
Costs screening			
• LDCT	€241.23 (€157.26 + €31.90 + €52.07)	Fixed	Nomenclature
• Follow-up scan***	€278.13 (€241.23 + €36.90)	Fixed	Nomenclature + information hospital pharmacist

* Some patients died after providing informed consent and before the randomization date.¹⁰ ** There are no further costs or effects linked to a negative screening result. *** The repeat scans which were performed in between the regular screening rounds in participants who had an indeterminate result in one of the regular scans were defined as follow-up scans.²²⁵

In the scientific literature of the NELSON trial, data were mainly published for male participants. For our analysis, we prefer to include information for all participants whenever possible. We received information on the participation rate, indeterminate and positive findings upon request from the NELSON investigators, separately for men and women, as well as for the entire NELSON population (see Table 46).

In the total NELSON population, 7557, 7294 and 6921 LDCT scans were performed over the first three screening rounds, respectively. Screening uptake was between 91.5% and 95.7%. Based on expert opinion, the screening uptake was reduced to 50% in the second and third round (Scenario 'adherence'). This would reflect the situation in which persons would mainly accept the first screening invitation, but adherence for further

screening rounds would be strongly reduced. This is only an explorative scenario analysis and in the base case the evidence from the NELSON trial is reflected.

The LDCT screening test can have three possible results, depending on the presence of nodules, nodule volume and volume doubling time (VDT):^y negative, indeterminate or positive.⁹³ The percentage of indeterminate tests was the highest (19.2%) during the first screening round and decreased to almost 7% for the second and third screening round. In the end, 185, 120 and 156 CT scans were test-positive during the three screening rounds, respectively. We note that the number of positive tests includes the indeterminate tests that were labelled positive after a repeat scan.^z

^y The volume determined the screening result: <50 mm³ was negative, 50–500 mm³ was indeterminate and >500 mm³ was positive.^{93, 226, 229, 234, 235, 236} In case of previously detected nodules, evaluation was based on growth (defined as change in volume) and VDT. If volume growth was <25%, the screening result was negative, and if the volume growth was ≥25%, the VDT of the nodule was calculated: for nodules with VDT of 400–600 days, the result was indeterminate, and the result was positive if the VDT was <400

days and/or a new solid component emerged in a previously non-solid nodule.²²⁹

^z This is confirmed by the detailed information described for the fourth round in the publication of Yousaf-Khan et al.²²⁹ After the first scan, there were 86 positive and 101 indeterminate findings. After performing the follow-up scan, there were 105 positive test results. This is the number of positive test results shown for the fourth round for men and women in Table 46.

**Table 46 – Participation rate and LDCT test results (NELSON trial – men and women)**

Variable	Screening uptake (participation rate)	Indeterminate	Positive
Men and women			
Round 1	7557/7899* (95.7%)	1451/7557 (19.2%)	185/7557 (2.4%)
Round 2	7294/7756* (94.0%)	480/7294 (6.6%)	120/7294 (1.6%)
Round 3	6921/7565* (91.5%)	471/6921 (6.8%)	156/6921 (2.3%)
Round 4	5279/6948 (76.0%)	101/5279 (1.9%)	105/5279 (2.0%)
Total	27 051/30 168 (89.7%)	2503/27 051 (9.3%)	566/27 051 (2.1%)
Men only			
Round 1	6309/6583 (95.8%)	1241/6309 (19.7%)	147/6309 (2.3%)
Round 2	6086/6459 (94.2%)	357/6086 (5.9%)	95/6086 (1.6%)
Round 3	5768/6285 (91.8%)	385/5768 (6.7%)	136/5768 (2.4%)
Round 4	4437/5771 (76.9%)	86/4437 (1.9%)	89/4437 (2.0%)
Total	22 600/25 098 (90.0%)	2069/22 600 (9.2%)	467/22 600 (2.1%)
Women only			
Round 1	1248/1316 (94.8%)	210/1248 (16.8%)	38/1248 (3.0%)
Round 2	1208/1297 (93.1%)	123/1208 (10.2%)	25/1208 (2.1%)
Round 3	1153/1280 (90.1%)	86/1153 (7.5%)	20/1153 (1.7%)
Round 4	842/1177 (71.5%)	15/842 (1.8%)	16/842 (1.9%)
Total	4451/5070 (87.8%)	434/4451 (9.8%)	99/4451 (2.2%)

Source: information received from the NELSON investigators. The data mentioned in non-italics are the data used in the economic model (information from the first three rounds for men and women together). * The denominator decreases due to participant deaths, withdrawals, lung cancer detections among participants, or administrative errors.²³⁷



In case of a **negative result**, people are invited for the next screening round (see part 6.1.7.1) until the end of the screening programme. No further incremental costs or effects are modelled after a negative test result.

A **positive result** leads to a referral to a pulmonologist for a diagnostic workup (see part 6.1.7.3).

An **indeterminate result** leads to an invitation for a repeat scan/follow-up scan (after 6–8 weeks or after 12 months, depending on nodule size and screening round) in order to classify the final result as positive or negative, based on volume change (growth) and growth rate, expressed in VDT.⁹³ In the model, we assume that the repeat scan is done in the same period as the first scan and that the same time period is applied to discount the cost of performing this repeat scan.

A publication of Yousaf-Khan et al.²²⁹ provides details about the fourth screening round, including what happens after an indeterminate finding. Such information was not identified for the first three screening rounds. From the 101 indeterminate findings in the fourth screening round, seven participants received no follow-up scan: *“two participants declined further screening, one participant did not respond anymore and four participants had an indeterminate screening result but were accidentally not invited for a follow-up scan. Hence, for these seven participants the final screening outcome remained indeterminate.”*²²⁹ On the other hand, some extra follow-up scans were performed: *“four participants with a negative regular scan result received accidentally a follow-up scan. Their screening results remained negative; In the follow-up scan one participant received an indeterminate result, so the participant received a second follow-up scan: the final scan was negative; From one participant the scan data were lost, the participant received a new follow-up scan. The final screening result was negative.”*²²⁹ In the end, the authors mention 101 follow-up scans were performed, i.e., exactly the same number as the original number of indeterminate findings. Therefore, we judged it is justified to include the exact same number of extra follow-up scans as the number of indeterminate findings for the first three screening rounds.

Cost information

In the NELSON trial, apart from local readings, all images were analyzed centrally with the use of semiautomated software.¹⁰ If the software was not able to segment a nodule accurately, the volume was corrected manually by the radiologist.²³⁸ Unlike a diagnostic CT scan, LDCT does not require contrast medium, so there are no costs associated with contrast.

In Belgium, there is no difference in nomenclature between low and normal-dose CT examinations. Nor is the workload of an examination determined by dose. The current nomenclature includes the examination and the reporting. The cost for the government and the patient together amounts to €157.26. On top of that, there is also the cost for the honorarium and a lump-sum for imaging of €31.90 and €52.07, respectively. The description of these nomenclature codes is as follows:

- Nomenclature code 459550: €157.26 (description: “Computed tomography of the thorax with or without contrast agent, with registration and clichés, minimum 15 sections, for the whole examination”)
- Nomenclature code 460795: €31.90 (description: “Consultation fee of accredited medical specialist for X-ray diagnosis, ...”)
- Nomenclature code 461016: €52.07 (description: “Lump-sum fee per prescription and per day for all technical medical imaging services provided on an outpatient basis ...”)

The question is whether for LDCT screening these nomenclature numbers will be used or if a new nomenclature code will be generated if, e.g., there is a central reading of the results with the support of one general algorithm. The total cost of this process may differ from the total cost of the previous three nomenclature codes. Since it is not clear whether this cost would be different we take into account the cost of the current nomenclature in the economic model.



In the NELSON trial, according to the protocol,²²⁵ double reading of the CT scan images was foreseen in the original protocol, and applied in three screening rounds. After evaluation,²³⁵ this was not performed anymore in the 4th round because of limited added value. According to the consulted experts, this would also be the case if lung cancer screening would be implemented in real life. Therefore, in the economic model, no extra costs are taken into account for double reading.

In case of **indeterminate test results**, a repeat scan is performed. Based on expert input, it was indicated that this would be a normal-dose CT scan using contrast medium. The cost for a repeat scan is the same, in the sense

that there is no difference between a low-dose examination and a normal-dose examination. An estimate of the cost for the contrast agent was provided by a hospital pharmacist: €36.90 for 100mL Iomeron 350^{aa} (RIZIV – INAMI code: 00807928). This cost is added to the additional test after an indeterminate finding.

6.1.7.3. *Diagnosis screening group (true and false positives and interval cancers)*

An overview of the input variables related to the true and false positive findings and interval cancers is presented in Table 47.

Table 47 – Overview of input variables diagnosis – true and false positive findings and interval cancers (NELSON trial – men and women)

Variable	Value	Uncertainty	Source
True and false positive findings			
• 1 st round			
○ True positive	70*/185	Beta (70; 115) (37.8%)	NELSON investigators
○ False positive	115/185	1 – true positive (62.2%)	
• 2 nd round			
○ True positive	55*/120	Beta (55; 65) (45.8%)	NELSON investigators
○ False positive	65/120	1 – true positive (54.2%)	
• 3rd round			
○ True positive	75*/156	Beta (75; 81) (48.1%)	NELSON investigators
○ False positive	81/156	1 – true positive (51.9%)	
Interval cancers*			
• 1 st round			
○ First year	5	Beta (5; 7552**)	Yousaf-Khan et al. ²²⁹

^{aa} This is in line with the information retrieved from the article 'best protocol for combined contrast-enhanced thoracic and abdominal CT for lung cancer'²³⁹ in which it is stated that all patients received a standardized IV injection

through a power injector consisting of iomeprol (Iomeron, Bracco) with either 350 or 400 mg I/mL at a dose of 0.5 g I/kg body weight. 0.5g I/kg body weight with Iomeron 350mg I/ml in an average person of about 70kg results in a dose of 100ml.



• 2nd round				
○ First year	7		Beta (19; 7275)	Yousaf-Khan et al. ²²⁹
○ Second year	12			
• 3rd round				
○ First year	7		Beta (11; 6910)	Yousaf-Khan et al. ²²⁹
○ Second year	4*			
○ <i>Last six months</i>	16			
Costs diagnosis				
• Diagnosis costs true positive	See part 6.1.7.10			
• Diagnosis costs false positive	€2527	Beta distributions for the probability of receiving one of the following interventions: van't Westeinde et al. ^{70, 71} and Belgian cost data		
		• Bronchoscopy: Beta (135; 106) • Mediastinoscopy: Beta (2; 225) • Lung surgery: Beta (47; 180)		
		Scenario 'supplements': €2752		
		Details: see Table 49		

* In the above table, we refer to the number of participants with screening-detected or interval lung cancer. In the article of Yousaf-Khan et al.,²²⁹ an overview of screening-detected lung cancers and interval cancers across the screening rounds is presented. A number of 74, 58 and 77 detected lung cancers is presented instead of 70, 55 and 75 for the first three screening rounds. The authors remark this is because the number of detected lung cancers does not equal the number of participants with lung cancers. Several participants are diagnosed with synchronous double tumours (round 1: n=4; round 2: n=3; round 3: n=2). Taking this into account, the numbers of participants are correct. This was also the case for one participant with an interval lung cancer (round 3, second year). As a result, the 5 interval cancers reported by Yousaf-Khan et al.²²⁹ for the second year of the 3rd round refers to 4 participants.

** the second parameter of the Beta distribution reflects the sample size minus the number of cases (e.g., 7552 = 7557-5).



People with a **positive screening result** were informed about their referral to a pulmonologist.²²⁵ A true positive (TP) test result was defined as a positive result in a participant diagnosed with lung cancer after workup by a pulmonologist. A false positive (FP) test result was defined as a positive result in a participant when lung cancer was not diagnosed after referral to a pulmonologist for a diagnostic workup.²²⁵ The number of true and false positive tests for men and women in the NELSON trial is shown per screening round in Table 48. In the first screening round, 37.8% (70/185) of positive screening tests were true positive findings. In the second and third round, this was 45.8% (55/120) and 48.1% (75/156), respectively.

Next to screen-detected lung cancers, there are also interval lung cancers. These are defined as: "1) *diagnosed after a negative screening test and before a next regular screening round*; 2) *lung cancers diagnosed after an indeterminate screening test, without a follow-up CT scan before the next regular screening round*; or 3) *or lung cancers diagnosed after a positive screening result if the diagnostic workup initiated for the positive screening result did not yield a diagnosis of lung cancer, and the diagnosis was made later because symptoms had triggered diagnostic assessment that eventually yielded diagnosis of lung cancer.*"²²⁵ The number of participants with an interval lung cancer are extracted from the publication of Yousaf-Khan et al.²²⁹ and are presented in Table 47. As previously mentioned (see part 6.1.5), in the third screening round, the number of interval cancers was much higher at an interval of 2.5 years. This was an indication to experts that the duration of this screening interval was too long. In the economic evaluation, the third screening round is reduced to two years, excluding the 16 additional interval cancers identified after this period.

Table 48 – True and false positive findings (NELSON trial – men and women)

Variable	Positive test results	Detection of lung cancer (true positive)	False positive findings
Men and women			
Round 1	185	70	115
Round 2	120	55	65
Round 3	156	75	81
<i>Round 4</i>	<i>105</i>	<i>43</i>	<i>62</i>
Total	566	243	323
Men only			
Round 1	147	56	91
Round 2	95	45	50
Round 3	136	65	71
<i>Round 4</i>	<i>89</i>	<i>37</i>	<i>52</i>
Total	467	203	264
Women only			
Round 1	38	14	24
Round 2	25	10	15
Round 3	20	10	10
<i>Round 4</i>	<i>16</i>	<i>6</i>	<i>10</i>
Total	99	40	59

Source: information received from the NELSON investigators.

The data not mentioned in italics are the data used in the economic model (information from the first three rounds for men and women together).



Cost information

For diagnostic costs, we distinguish between true positive and false positive findings.

In case of true positive findings, we rely on the real-world Belgian data as presented in the previous chapter. The BCR database contains information from patients diagnosed with lung cancer, as in true positive findings. Details on these costs are presented in part 5.3.2.

To estimate the costs of false positive evaluations, data from van't Westeinde et al.⁷¹ regarding work-up of screen-positive participants in the NELSON trial were combined with Belgian billing codes. Using information presented in Figure 3 from this publication, the number of participants receiving (non-) surgical work-up and the proportion of benign outcomes (thus representing false positives) could be reconstructed. Note that at the top of the figure in this publication, the number of screen-positive participants should be n=415 instead of n=215. The non-invasive work-up is described as the following: *"Subjects with a positive test result were referred for work-up to a pulmonologist and, depending on the outcome of this work-up, a resection of the suspicious lesion was performed. The standard non-invasive work-up included a physical exam, pulmonary function test, bronchoscopy, FDG-PET-scan and a standard-dose CT scan with intravenous contrast of the chest and upper abdomen."*⁷¹ The number of bronchoscopies was retrieved in another publication by van't Westeinde et al.⁷⁰ To estimate the costs of lung surgery for a false positive result (47 surgeries in the NELSON sample, of which the majority by thoracotomy and a small number by VATS), we used the Belgian data to calculate the mean cost of the hospitalization during which the procedure '227264 – Total or partial lung exeresis' was billed. This was performed on a sample of stage I lung cancer patients. Of note, in the NELSON sample the overall median length of hospital stay was 13 days (2-51 days) after thoracotomy and 8 days (4-12 days) after VATS. In the Belgian sample, the mean length of stay was 10.7 days. In the end, the total costs included in the model sum up to an average of €1865.17 in the base case (see Table 49). In a scenario analysis, the supplements linked to the lung surgery are also taken into account (Scenario 'supplements').

If a workup after a positive screening did not lead to lung cancer diagnosis, participants were invited for the next screening round.²²⁹

We note that we do not include costs for the diagnosis of interval cancers. This is because we assume that interval cancers occur at the same rate in both the intervention and comparator arm and thus do not generate incremental costs or effects (see part 6.1.7.7).



Table 49 – Costs of false positive evaluations based on the NELSON trial

Costs of false positive evaluations in NELSON sample (n=227)			
Non-invasive and invasive work-up	Billing code	Number*	Cost/unit (01/01/2024)
Physical exam - pulmonologist consultation (x2)	102631 - Raadpleging in de spreekkamer door een geaccrediteerde arts-specialist in de pneumologie, inclusief een verplicht schriftelijk verslag aan de behandelende arts	454	€52.44
Pulmonary function test	471251 - Volledige spirografie met bepalen van maximum adem minuten volume	227	€14.21
	471310 - Bepalen van het residuair volume		€56.86
	471354 - Meten van diffusiecapaciteit		€56.86
FDG-PET-scan and a standard-dose CT scan with intravenous contrast	442971 - Positronentomografisch onderzoek door coïncidentiedetectie met protocol en documenten, voor het geheel van het onderzoek	227	€209.23
	747810 - Fludeoxyglucose (F-18)		€60
	459896 - Computergestuurde tomografie met registreren en clichés, met of zonder contrastmiddel, tegelijkertijd uitgevoerd bij een PET onderzoek dat tenminste een opname van de halsregio tot en met het abdomen omvat, voor diagnostische doeleinden		€275.20
	Cost for the intravenous contrast (see part 6.1.7.2)		€36.90
Bronchoscopy**	471730 - Bronchoscopie met afname voor biopsie, en/of verwijderen van tumors, en/of coagulatie van letsels	67.5	€159.89
	471855 - Echo-endoscopie van de bronchi met punctie van extramuraal weefsel	67.5	€1866
	(Estimated cost of ambulatory stay provided by medical expert)		
Mediastinoscopy	228152 - Mediastinoscopie	2	€255.25
Lung surgery	227264 - Totale of gedeeltelijke long-exeresis	47	€5219.42***
	(Cost of hospitalization calculated using Belgian data)		€6306.24*** (+supplements)
	101290 - Raadpleging in de spreekkamer door een geaccrediteerde arts-specialist in de heelkunde, inclusief een eventueel schriftelijk verslag aan de behandelende arts		€35.08



	105475 - Raadpleging in de spreekkamer door een geaccrediteerde arts-specialist in de anesthesie en reanimatie, inclusief een eventueel schriftelijk verslag aan de behandelende arts	€31.81
	102594 - Raadpleging in de spreekkamer door een geaccrediteerde arts-specialist in de cardiologie, inclusief een eventueel schriftelijk verslag aan de behandelende arts	€47.47
	475075 - Elektrocardiografische onderzoeken, met protocol, ten minste 12 verschillende derivaties	€20.79
TOTAL		€2527 (excl. supplements)
(Mean cost per false positive)		€2752 (incl. supplements)

* Source: data retrieved from van't Westeinde et al.^{70, 71} ** Number of bronchoscopies performed for false positives retrieved from Figure 1 in van't Westeinde et al.⁷⁰ Of note, the number of bronchoscopies performed in NELSON is between 130 and 140 - we assumed a number of 135. According to the input of a Belgian medical expert, about half of these bronchoscopies would be standard bronchoscopies, whereas the other half would be performed using echobronchoscopy. *** Cost of hospitalization calculated using Belgian data.

6.1.7.4. Diagnosis (stage and histology)

An overview of the input variables related to the staging and histology is presented in Table 50.

Table 50 – Overview of input variables diagnosis – stage and histology (NELSON trial – men and women)

Variable	Value	Uncertainty	Source
Stages screen-detected cancers*			
• 1 st round			
		Conditional beta distributions:	Yousaf-Khan et al. ²²⁹
○ Stage I	48/74*	$\pi_1 = \text{Beta} (48; 26) (64.9\%)$	
○ Stage II	7/74	$\pi_2 = (1 - \pi_1)[\text{Beta} (7; 19)] (9.5\%)$	
○ Stage III	14/74	$\pi_3 = (1 - \pi_1 - \pi_2)[\text{Beta} (14; 5)] (18.9\%)$	
○ Stage IV	5/74	$\pi_4 = (1 - \pi_1 - \pi_2 - \pi_3) (6.8\%)$	
• 2 nd round			
		Conditional beta distributions:	Yousaf-Khan et al. ²²⁹
○ Stage I	44/58*	$\pi_1 = \text{Beta} (44; 14) (75.9\%)$	
○ Stage II	4/58	$\pi_2 = (1 - \pi_1)[\text{Beta} (4; 10)] (6.9\%)$	
○ Stage III	8/58	$\pi_3 = (1 - \pi_1 - \pi_2)[\text{Beta} (8; 2)] (13.8\%)$	
○ Stage IV	2/58	$\pi_4 = (1 - \pi_1 - \pi_2 - \pi_3) (3.4\%)$	



Variable	Value	Uncertainty	Source
• 3rd round			
○ Stage I	56/77*	Conditional beta distributions: $\pi_1 = \text{Beta} (56; 21) (72.7\%)$ $\pi_2 = (1 - \pi_1)[\text{Beta} (3; 18)] (3.9\%)$ $\pi_3 = (1 - \pi_1 - \pi_2)[\text{Beta} (15; 3)] (19.5\%)$ $\pi_4 = (1 - \pi_1 - \pi_2 - \pi_3) (3.9\%)$	Yousaf-Khan et al. ²²⁹
○ Stage II	3/77		
○ Stage III	15/77		
○ Stage IV	3/77		
Stages interval cancers			
• 1 st round			
○ Stage I	0/5	Conditional beta distributions: / / $\pi_1 = \text{Beta} (1; 4) (20\%)$ $\pi_2 = (1 - \pi_1) (80\%)$	Horeweg et al. ²²⁴
○ Stage II	0/5		
○ Stage III	1/5		
○ Stage IV	4/5		
• 2 nd round			
○ Stage I	1/19	Conditional beta distributions: $\pi_1 = \text{Beta} (1; 18) (5.3\%)$ $\pi_2 = (1 - \pi_1)[\text{Beta} (1; 17)] (5.3\%)$ $\pi_3 = (1 - \pi_1 - \pi_2)[\text{Beta} (3; 14)] (15.8\%)$ $\pi_4 = (1 - \pi_1 - \pi_2 - \pi_3) (73.7\%)$	Horeweg et al. ²²⁴
○ Stage II	1/19		
○ Stage III	3/19		
○ Stage IV	14/19		
• 3 rd round			
○ Stage I	2/11	Conditional beta distributions: $\pi_1 = \text{Beta} (2; 9) (18.2\%)$ $\pi_2 = (1 - \pi_1)[\text{Beta} (2; 7)] (18.2\%)$ $\pi_3 = (1 - \pi_1 - \pi_2)[\text{Beta} (1; 6)] (9.1\%)$ $\pi_4 = (1 - \pi_1 - \pi_2 - \pi_3) (54.5\%)$	Horeweg et al. ²²⁴
○ Stage II	2/11		
○ Stage III	1/11		
○ Stage IV	6/11		
Stages control group			
○ Stage I	53/345**	Conditional beta distributions: $\pi_1 = \text{Beta} (53; 292) (15.4\%)$ $\pi_2 = (1 - \pi_1)[\text{Beta} (37; 255)] (10.7\%)$ $\pi_3 = (1 - \pi_1 - \pi_2)[\text{Beta} (94; 161)] (27.2\%)$ $\pi_4 = (1 - \pi_1 - \pi_2 - \pi_3) (46.7\%)$	NELSON investigators
○ Stage II	37/345		
○ Stage III	94/345		
○ Stage IV	161/345		
Histology screen-detected cancers			
• 1 st round			



Variable	Value	Uncertainty	Source
○ NSCLC ○ SCLC ○ Others	54/74 1/74 19/74	$\pi_1 = \text{Beta}(54; 1)$ (98.2%) $\pi_2 = (1 - \pi_1)$ (1.8%) /***	Yousaf-Khan et al. ²²⁹
• 2 nd round			
○ NSCLC ○ SCLC ○ Others	41/58 2/58 15/58	$\pi_1 = \text{Beta}(41; 2)$ (95.3%) $\pi_2 = (1 - \pi_1)$ (4.7%) /***	Yousaf-Khan et al. ²²⁹
• 3 rd round			
○ NSCLC ○ SCLC ○ Others	59/77 5/77 13/77	$\pi_1 = \text{Beta}(59; 5)$ (92.2%) $\pi_2 = (1 - \pi_1)$ (7.8%) /***	Yousaf-Khan et al. ²²⁹
Histology interval cancers			
• 1 st round			
○ NSCLC ○ SCLC ○ Others and unknown	4/5 0/5 1/5	100% 0% /***	Horeweg et al. ²²⁴
• 2 nd round			
○ NSCLC ○ SCLC ○ Others and unknown	10/19 7/19 2/19	$\pi_1 = \text{Beta}(10; 7)$ (58.8%) $\pi_2 = (1 - \pi_1)$ (41.2%) /***	Horeweg et al. ²²⁴
• 3 rd round			
○ NSCLC ○ SCLC ○ Others and unknown	7/11 0/11 4/11	100% 0% /***	Horeweg et al. ²²⁴

* In the article of Yousaf-Khan et al.,²²⁹ the authors refer to the number of detected lung cancers. This does not equal the number of participants with lung cancer since some of them are diagnosed with synchronous double tumours (round 1: n=4; round 2: n=3; round 3: n=2).

** As shown in Table 51, there are 19 unknown cases in the control group. As such the denominator becomes 364 – 19 = 345.

*** Since there are no details for this group, we do not explicitly include them. This way, they are implicitly evenly distributed between the NSCLC and SCLC categories.



The diagnosed cancers (both true positive findings and interval cancers) are categorized according to stage and histology. Including the evidence on stage and histology in the economic evaluation is important because this has an impact on both costs and effects. In the NELSON trial, *“the first recorded diagnosis of lung cancer and prevailing TNM-classification, stage and histology (6th edition for 2003-2009 diagnoses or 7th edition for 2010-2016 diagnoses) were used as provided by the Dutch and Belgian national cancer registries. In case of a double tumor with an equal incidence date, the lung cancer with the highest stage was included. ... The histology was classified into adenocarcinoma, squamous cell carcinoma, small cell carcinoma, non-small cell carcinoma, and others using the International Classification of Diseases for Oncology, Third Edition (ICDO-3).”*^{240,225}

Table 51 presents the stage distribution for screen and non-screen detected lung cancers in the intervention group, as well as for any lung cancer in both the intervention and control group. This information was received from the NELSON investigators and reports the information aggregated for the 4 screening rounds. For the intervention group, we preferred to include the more detailed information presented in the publication of Yousaf-Khan et al.,²²⁹ in which the staging is reported disaggregated for the four screening rounds (see Table 52). For the interval cancers, staging information is presented by Horeweg et al.,²²⁴ as presented in Table 53. In this study, results are presented separately for interval cancers in the first and second year after screening. This allows us to include only the information for interval cancers up to 5 years (see part 6.1.5). In our economic evaluation,

the numbers for the first and second year after screening are combined for the second and third screening round (not relevant for the first screening round in which the screening interval was only 1 year).

For the comparator group, no disaggregated information is available per screening round. Therefore, we use the staging information for the 364 lung cancers in the control group presented in Table 51.

The majority of the screen-detected lung cancers are stage I lung cancers, 65%, 76% and 73%, respectively in the three screening rounds. The interval cancers are mainly stage IV (80%, 74%, and 55%, respectively in the three screening rounds). In the control group, about 15% are stage I lung cancers, while about 47% are detected as stage IV lung cancers.

Note that in the publication of Yousaf-Khan et al.,²²⁹ information is presented for 74, 58, and 77 screening-detected lung cancers in the first, second and third screening round, respectively. This reflects information for 70, 55 and 75 patients, respectively, due to the presence of synchronous double tumours in several patients, and explains the difference between the numbers of true positive findings in Table 47 and the denominator for the stage distribution mentioned in Table 50 (or the number of screening-detected lung cancers in Table 52). In the economic model, the stage distribution is applied to the number of patients with lung cancer. Furthermore, in the economic model, stages Ia and Ib, IIa and IIb, IIIa and IIIb are combined to stages I, II and III, respectively. This is because utilities and cost information is also available according to the four stages.


Table 51 – Stage distribution for screen and non-screen detected lung cancers (N (%)) (NELSON trial – men and women – 4 screening rounds)

	Screen-detected	Screening group Non-screen detected	Any lung cancer	Control group Any lung cancer
Men and women				
Stage IA	124 (51.0%)	14 (7.8%)	138 (32.7%)	29 (8.0%)
Stage IB	28 (11.5%)	11 (6.1%)	39 (9.2%)	24 (6.6%)
Stage IIA	11 (4.5%)	6 (3.4%)	17 (4.0%)	17 (4.7%)
Stage IIB	11 (4.5%)	6 (3.4%)	17 (4.0%)	20 (5.5%)
Stage IIIA	23 (9.5%)	21 (11.7%)	44 (10.4%)	49 (13.5%)
Stage IIIB	13 (5.3%)	20 (11.2%)	33 (7.8%)	45 (12.4%)
Stage IV	19 (7.8%)	88 (49.2%)	107 (25.4%)	161 (44.2%)
Unknown	14 (5.8%)	12 (6.7%)	26 (6.2%)	19 (5.2%)
Missing	0 (0.0%)	1 (0.6%)	1 (0.2%)	0 (0.0%)
Total	243	179	422	364
Men only				
Stage IA	95 (46.8%)	10 (7.1%)	105 (30.5%)	21 (6.9%)
Stage IB	24 (11.8%)	10 (7.1%)	34 (9.9%)	20 (6.6%)
Stage IIA	8 (3.9%)	4 (2.8%)	12 (3.5%)	13 (4.3%)
Stage IIB	11 (5.4%)	6 (4.3%)	17 (4.9%)	17 (5.6%)
Stage IIIA	20 (9.9%)	14 (9.9%)	34 (9.9%)	43 (14.1%)
Stage IIIB	13 (6.4%)	14 (9.9%)	27 (7.8%)	34 (11.2%)
Stage IV	19 (9.4%)	73 (51.8%)	92 (26.7%)	139 (45.7%)
Unknown	13 (6.4%)	10 (7.1%)	23 (6.7%)	17 (5.6%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	203	141	344	304
Women only				
Stage IA	29 (72.5%)	4 (0.0%)	33 (0.0%)	8 (13.3%)



	Screen-detected	Screening group Non-screen detected	Any lung cancer	Control group Any lung cancer
Stage IB	4 (10.0%)	1 (0.0%)	5 (0.0%)	4 (6.7%)
Stage IIA	3 (7.5%)	2 (0.0%)	5 (0.0%)	4 (6.7%)
Stage IIB	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.0%)
Stage IIIA	3 (7.5%)	7 (0.0%)	10 (0.0%)	6 (10.0%)
Stage IIIB	0 (0.0%)	6 (0.0%)	6 (0.0%)	11 (18.3%)
Stage IV	0 (0.0%)	15 (0.0%)	15 (0.0%)	22 (36.7%)
Unknown	1 (2.5%)	2 (0.0%)	3 (0.0%)	2 (3.3%)
Missing	0 (0.0%)	1 (0.0%)	1 (0.0%)	0 (0.0%)
Total	40	38	78	60

Source: information received from the NELSON investigators.

Table 52 – Stage distribution of screening-detected lung cancers of all rounds (NELSON trial – men and women)

	Round 1			p Value*	Round 2			p Value†	Round 3			p Value‡	Round 4		
	n	Per cent	Cumulative %		n	Per cent	Cumulative %		n	Per cent	Cumulative %		n	Per cent	Cumulative %
				0.37				0.02				0.10			
Stage															
Ia	44	59.5	59.5		43	74.1	74.1		50	64.9	64.9		22	47.8	47.8
Ib	4	5.4	64.9		1	1.7	75.9		6	7.8	72.7		6	13.0	60.9
IIa	7	9.5	74.3		4	6.9	82.8		–	–	76.6		3	6.5	67.4
IIb	–	–	–		–	–	–		3	3.9	–		4	8.7	76.1
IIIa	10	13.5	87.8		6	10.3	93.1		14	18.2	94.8		3	6.5	82.6
IIIB	4	5.4	93.2		2	3.4	96.6		1	1.3	96.1		2	4.3	87.0
IV	5	6.8	100		2	3.4	100		3	3.9	100		6	13.0	100
Total	74	100	–		58	100	–		77	100	–		46	100	–

*p Value: comparison of stage distribution of the screening-detected lung cancers of round 1 vs round 4.

†p Value: comparison of stage distribution of the screening-detected lung cancers of round 2 vs round 4.

‡p Value: comparison of stage distribution of the screening-detected lung cancers of round 3 vs round 4.

Source: Table 3 from publication of Yousaf-Khan et al.²²⁹

**Table 53 – Stage distribution of interval cancers (NELSON trial (Dutch part) – 3 screening rounds)**

	Round 1	Round 2*	Round 3*
Stage IA	0	1 (5.3%)	2 (18.2%)
Stage IB	0	0	0
Stage IIA	0	0	0
Stage IIB	0	1 (5.3%)	2 (18.2%)
Stage IIIA	0	3 (15.8%)	0
Stage IIIB	1 (20%)	0	1 (9.1%)
Stage IV	4 (80%)	14 (73.7%)	6 (54.5%)
Total	5	19	11

Source: Horeweg et al.²²⁴

Remark: The study of Horeweg et al.²²⁴ presents information for the 7438 Dutch participants of the NELSON trial and excluded 477 Belgian patients. However, since the total number of interval cancers equals the number of interval cancers for the full population, no adjustments were needed. * In the study of Horeweg et al.,²²⁴ results are presented separately for interval cancers in the first and second year after screening. In the above table, these numbers are combined.

In the economic model, lung cancers are characterised not only by stage but also by histology. As with the information on stages, we received data from the NELSON investigators (Table 54), and disaggregated data are available by screening round in the references of Yousaf-Khan et al.²²⁹ (screening-detected lung cancers – Table 55) and Horeweg et al.²²⁴ (interval cancers – Table 56).

The vast majority of screen-detected lung cancers are NSCLC: 98.2%, 95.3%, and 92.2% in the first three rounds, respectively. For the interval cancers, this was 100%, 58.8% and 100%, respectively. However, we note that the latter percentages for interval cancers are based on small samples.

In the economic model, we make the assumption that there is no correlation between lung cancer stages and histology. This further disaggregation would create too many 'small cells' with multiple zero values. The focus is initially to reflect the evidence on the total number of modelled cancers and stages. Afterwards, we try to do the same for histology (see part 6.1.9 – model validation). The reason we initially look at stages is because the impact on costs and effects is mainly associated with the stage shift (after excluding overdiagnosis – see part 6.1.7.7). The impact of screening is the earlier detection of cancer, not that a cancer's histology would change.

**Table 54 – Histology of screen and non-screen detected lung cancers (N (%)) (NELSON trial – men and women – 4 screening rounds)**

	Screen-detected	Screening group Non-screen detected	Any lung cancer	Control group Any lung cancer
Men and women				
Adenocarcinoma	156 (64.2%)	74 (41.3%)	230 (54.5%)	162 (44.5%)
Squamous-cell carcinoma	43 (17.7%)	40 (22.3%)	83 (19.7%)	105 (28.8%)
Small-cell carcinoma	13 (5.3%)	36 (20.1%)	49 (11.6%)	59 (16.2%)
NSCLC	8 (3.3%)	12 (6.7%)	20 (4.7%)	15 (4.1%)
Other	23 (9.5%)	16 (8.9%)	39 (9.2%)	23 (6.3%)
missing	0 (0.0%)	1 (0.6%)	1 (0.2%)	0 (0.0%)
Total	243	179	422	364
Men only				
Adenocarcinoma	123 (60.6%)	56 (39.7%)	179 (52.0%)	133 (43.8%)
Squamous-cell carcinoma	39 (19.2%)	38 (27.0%)	77 (22.4%)	94 (30.9%)
Small-cell carcinoma	13 (6.4%)	27 (19.1%)	40 (11.6%)	46 (15.1%)
NSCLC	8 (3.9%)	8 (5.7%)	16 (4.7%)	13 (4.3%)
Other	20 (9.9%)	12 (8.5%)	32 (9.3%)	18 (5.9%)
missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	203	141	344	304
Women only				
Adenocarcinoma	33 (82.5%)	18 (47.4%)	51 (65.4%)	29 (48.3%)
Squamous-cell carcinoma	4 (10.0%)	2 (5.3%)	6 (7.7%)	11 (18.3%)
Small-cell carcinoma	0 (0.0%)	9 (23.7%)	9 (11.5%)	13 (21.7%)
NSCLC	0 (0.0%)	4 (10.5%)	4 (5.1%)	2 (3.3%)
Other	3 (7.5%)	4 (10.5%)	7 (9.0%)	5 (8.3%)
missing	0 (0.0%)	1 (2.6%)	1 (0.0%)	0 (0.0%)
Total	40	38	78	60

Source: information received from the NELSON investigators.



Table 55 – Histology of screening-detected lung cancers of all rounds (NELSON trial – men and women)

	Round 1		p Value*	Round 2		p Value†	Round 3		p Value‡	Round 4	
	n	Per cent		n	Per cent		n	Per cent		n	Per cent
			0.01			0.001			0.06		
Histology											
Adenocarcinoma	35	47.3		35	60.3		37	48.1		23	50.0
Squamous cell carcinoma	15	20.3		3	5.2		16	20.8		10	21.7
BAC	2	2.7		3	5.2		6	7.8		4	8.7
SCLC	1	1.4		2	3.4		5	6.5		3	6.5
NSCLC, not specified	2	2.7		–	–		–	–		4	8.7
Others	19§	25.7		15¶	25.9		13**	16.9		2††	4.3
Total	74	100		58	100		77	100		46	100

*p Value: difference in histology between the first and last screening rounds. Fisher's exact test was used.

†p Value: difference in histology between the second and last screening rounds. Fisher's exact test was used.

‡p Value: difference in histology between the third and last screening rounds. Fisher's exact test was used.

§Others in round 1: 5 large cell carcinomas, 1 mixed NSCLC/SCLC, 4 carcinoids, 1 other, 3 no diagnosis was possible, 2 adenosquamous and 3 large-cell neuroendocrine carcinoma.

¶Others in round 2: 10 large-cell carcinomas, 2 adenosquamous cell carcinoma and 3 cancers without a diagnosis were included in the group of others; in round 4: 2 cancers without a possible diagnosis were included in the group of others.

**Others in round 3: 2 large-cell carcinomas, 1 mixed NSCLC/SCLC, 2 carcinoids, 1 large-cell neuroendocrine carcinoma and 7 without a diagnosis; in round 4: 2 cancers without a diagnosis.

††Others in round 4: 2 with no diagnosis possible. No other types of lung cancers were detected in this round.

BAC: bronchoalveolar carcinoma; NSCLC, non-small cell lung carcinoma; SCLC: small-cell carcinoma.

Source: Table 4 from publication of Yousaf-Khan et al.²²⁹

**Table 56 – Histology of interval cancers (NELSON trial (Dutch part) – 3 screening rounds)**

	Round 1	Round 2*	Round 3*
Adenocarcinoma	1 (20%)	4 (21.1%)	4 (36.4%)
Squamous-cell Carcinoma	0	5 (26.3%)	1 (9.1%)
Bronchoalveolar Carcinoma	0	0	0
Small-cell Carcinoma	0	7 (36.8%)	0
Large-cell Carcinoma	3 (60%)	1 (5.3%)	2 (18.2%)
Other**	1 (20%)	1 (5.3%)	3 (27.3%)
Unknown	0	1 (5.3%)	1 (9.1%)
Total	5	19	11

Source: Horeweg et al.²²⁴

Remark: The study of Horeweg et al.²²⁴ presents information for the 7438 Dutch participants of the NELSON trial and excluded 477 Belgian patients. However, since the total number of interval cancers equals the number of interval cancers for the full population, no adjustments were needed. * In the study of Horeweg et al.,²²⁴ results are presented separately for interval cancers in the first and second year after screening. In the above table, these numbers are combined. ** Other histological subtypes of lung cancer were: adenosquamous carcinoma, mixed large-cell small-cell carcinoma, large-cell neuroendocrine carcinoma, carcinoid, mucinous carcinoma, pleiomorph carcinoma, non-small-cell lung carcinoma, or subtype not otherwise specified.²²⁴

6.1.7.5. Overdiagnosis

An overview of the input variables related to overdiagnosis is presented in Table 57.

Table 57 – Overview of input variables overdiagnosis

Variable	Value	Uncertainty	Source
Overdiagnosis (Ps*)		Scenario 'overdiagnosis'	
• Men only (5.5 years FU after last screen)	18/203**	Beta (18; 185) (8.9%)	NELSON trial ¹⁰
• Men only (4.5 years FU after last screen)	40/203**	Beta (40; 163) (19.7%)	NELSON trial ¹⁰
• Men and women (4.5 years FU after last screen)	58/243**	Beta (58; 185) (23.9%) = base case	NELSON investigators
• Meta-analysis (including 5 trials)	38% (95% CI 14-63%)	Beta (5.35; 8.73) (38%)	Brodersen et al. ⁷³

* Ps = proportion of screen-detected cases. ** In the NELSON trial, over the 4 screening rounds, there were 203 (men only) and 243 (men and women) screen-detected cases.



A potential bias that may be present in screening is overdiagnosis. As mentioned in the NELSON protocol, *“some cancers detected by screening are likely to be relatively slowly growing. Some of these screen-detected cancers would never have become clinically detected during lifetime in a scenario without screening. Another possibility is that a person with a screen-detected lung cancer dies from other causes. These situations reflect overdiagnosis, which can cause serious adverse physical and psychological effects, e.g., an increased period of knowing of having the disease and unnecessary treatment (overtreatment) with the accompanying side effects.”*²²⁵

In the clinical part, it is mentioned that two different measures of overdiagnosis were used, depending on the denominator used:

- Pa (proportion of all lung cancer cases): the ratio between excess incidence (calculated as the difference between the cumulative incidence of lung cancer in the screening and control arms) and the cumulative incidence of all lung cancers in the screening arm
- Ps (proportion of screen-detected cases): the ratio between excess incidence and the cumulative incidence of screen-detected lung cancers

The latter approach represents the risk that a screen-detected cancer is overdiagnosed. It is considered more suitable to inform individuals about the pros and cons of screening (see part 3.2.9) and is used in the NELSON trial.

In the NELSON trial, *“an excess of 40 cases (344 vs. 304) was found among the male participants in the screening group 10 years after randomization (4.5 years after the final screening round), which suggests an excess-incidence overdiagnosis rate of 19.7% (bootstrapped 95% CI, -5.2 to 41.6) for screening-detected cases. However, extending the follow-up to 11 years after randomization (5.5 years after the final screening round) reduced the number of excess cases to 18, yielding an excess-incidence overdiagnosis rate of 8.9% (bootstrapped 95% CI, -18.2 to 32.4) for screening-detected cases.”*¹⁰ According to the NELSON researchers, appropriate estimation of the level of overdiagnosis in the NELSON trial requires additional years of follow-up.²⁴¹ Because of this, the researchers state an overdiagnosis rate of 8.9% for screening-detected cases may be considered as the upper limit of overdiagnosis in the NELSON trial.¹⁰ In our economic model, the

overdiagnosis rates 10- and 11 years post randomization are both taken into account as scenarios (Scenario ‘overdiagnosis’).

Information was also received from the NELSON investigators for men and women separately and combined. As mentioned above, in men, an excess of 40 cases on 203 screening detected cancers was found. As shown in Table 51, in women, this was 18 cases on 40 screen detected cases (45%). The combination of men and women resulted in 58 cases out of 243 screen-detected cases (23.9%). For all previous input variables, we decided to include the information for both men and women (if available). Therefore, the latter percentage is included as the base case in the economic model.

Finally, meta-analyses were performed with studies comparing LDCT screening to no screening, thus excluding the NLST trial, and with a median follow-up of more than 10 years after randomization. The meta-analysis of Bonney et al. was excluded since they estimated overdiagnosis in relation to all individuals invited for screening (Pa). The meta-analysis of Brodersen et al.⁷³ provided a Ps estimate of 38% (CI 14-63%) (see part 3.2.9). This estimate is also included as a scenario (Scenario ‘overdiagnosis’).

6.1.7.6. Contamination rate

As described in the clinical part of the report, the background CT rate in Belgium should be taken into account as it biases the overdiagnosis estimate to the null. However, the contamination rate was not well described across trials (see Table 11). Baecke et al.⁷⁴ described contamination in the NELSON trial as *“examinations performed after randomization because of ‘precaution’ or ‘no examination was offered by NELSON”*. This study reported that in the first 24 months after randomization, 3.1% of the respondents in the no screening arm received a lung cancer screening examination.⁷⁴ This percentage did not differ from the background rates in the last 18 months before randomization. As the reported contamination rate was small and only determined at baseline, we did not include it in the economic evaluation. Since the contamination rate biases the overdiagnosis estimate to the null, its impact is indirectly included in the scenarios with different overdiagnosis estimates.



6.1.7.7. Modelled cancers in the intervention and control arm

The information presented in the previous parts is modelled in the following way to estimate the number of cancers in the intervention and control arm:

- For the intervention arm:
 1. per screening round, the number of screen-detected cancers and interval cancers is modelled
 2. per screening round, the number of screen-detected and interval cancers is divided over stages and histology
 3. per screening round, the percentage of overdiagnosis is applied to the number of screen-detected cancers to estimate the number of overdiagnosed cancers.
 4. The number of overdiagnosed cases is extracted from the group of stage I, NSCLC screen-detected cancers (see further).

Based on the above, three groups of cancers are created for each screening round in the intervention arm: a) screen-detected cancers, excluding overdiagnosis; b) overdiagnosed cancers; and c) interval cancers.

- For the control arm:
 5. the overdiagnosed cancers (group b) are not present in the control arm and are removed
 6. the remaining NSCLC and SCLC cancers (group a and c) are distributed among the stages according to the evidence-based stage distribution for the control arm

7. the interval cancers (group c) are assumed to be equal in the intervention and control arm and are presented separately.

Based on the above, two groups of cancers are created for each screening round in the control arm: d) cancers which are not overdiagnosed nor interval cancers and where a stage shift has an incremental impact; and group e) interval cancers (= group c).

In the NELSON protocol, it is mentioned that the biological behavior of very small lung cancers detected by spiral CT-scan is yet unknown, but the smaller the tumour is, the higher the risk of overdiagnosis.²²⁵ Therefore, and also for the simplicity of the model, we assume that overdiagnosis comes entirely from the largest group of cancers: stage I, NSCLC. This has no impact on the cost of the model as costs are taken into account both for overdiagnosis and for screen-detected cancers outside overdiagnosis. However, there is potentially an impact on the gain in QALYs modelled via the stage shift. When validating our results, we check whether the model potentially results in an over- or underestimate of the life years gained (see part 6.1.9).

Since the interval cancers are assumed equal in the intervention and control arm, there is no incremental impact on costs or effects. Nevertheless, in our model we had to include these cancers initially because the information for the control arm is only available for all cancers. With the approach discussed above, we were able to ensure that the stages for the modelled cancers were correct for both the intervention and the control group and reflect the available evidence (see part 6.1.9). Given the lack of an incremental impact, the interval cancers are not further elaborated in the model. For the other groups, however, there is a link to costs and effects that is explained in the following sections. The above is summarized in Table 58.

**Table 58 – Modelled cancers in the intervention and control group**

Lung cancer screening group	Control group
Screening detected cancers (group a + b) Per screening round, the percentage of stage I, II, III and IV screen-detected lung cancers reflects the evidence. Also the histology is modelled according to the available evidence (see part 6.1.7.4). • Overdiagnosis (group b) Extraction of overdiagnosis (see part 6.1.7.5) Assumption: overdiagnosed cancers are taken from the group of stage I NSCLC • Screen detected and no overdiagnosis (group a) Equals the screening detected cancers minus the overdiagnosed cancers. Remark: overdiagnosed cancers are linked to costs but do not generate positive effects. The remaining cancers are linked to the costs and effects, which are stage- and histology-specific. For the lung cancer-specific Belgian costs we refer to part 6.1.7.10. For the Belgian all-cause mortality according to stage and histology we refer to part 6.1.7.8. and for stage-specific utilities to part 6.1.7.9.	All identified cancers The stages of these cancers are modelled according to the identified evidence (see part 6.1.7.4) Overdiagnosis is not present in the control arm The interval cancers, as identified in the lung cancer screening arm (group c), are extracted from all identified cancers.
Interval cancers (group c) The percentage of stage I, II, III and IV interval cancers reflects the evidence (see part 6.1.7.4) Remark: the interval cancers are included up to 5 years (i.e., including 2-year time interval after the 3 rd screening round) Remark: In the economic evaluation, interval cancers are not linked to costs and effects since there is no incremental impact on these outcomes when comparing the lung cancer screening and control group	Interval cancers No difference assumed in interval cancers between the screening and control arm since these are not identified through screening.

NSCLC: non-small cell lung cancer. Remark: this approach is needed to be able to reflect the evidence. In the intervention arm, more details are available: i.e. stages and histology per screening round for both screening detected lung cancers and interval cancers separately. In the control arm, information is given for all identified cancers over all three screening rounds.



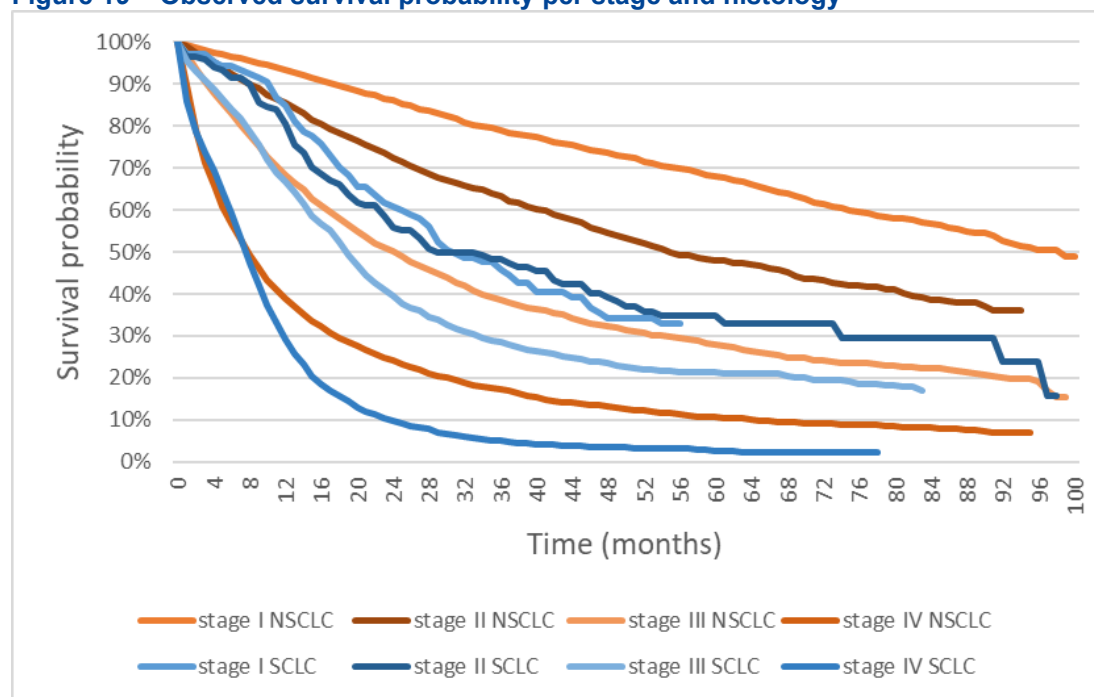
6.1.7.8. Mortality

In Belgium, reporting all newly diagnosed cancer cases to the Belgian Cancer Registry (BCR) is compulsory for hospitals and for pathology laboratories. Completeness of incidence has been estimated to be at least 98% of all cancer cases in Belgium from 2004 onwards.²²² The cancer registry database comprises, among others, the following patient and tumour characteristics: sex, age at diagnosis, incidence date (i.e. the date of first histopathological confirmation of the tumour or, if not available, the date of the technical procedure or clinical investigation leading to the

diagnosis of cancer), topography and histology of the tumour (ICD-O-3), and clinical and pathological TNM stage at diagnosis.² The Belgian Cancer Registry has a legal basis to use the patient's unique National Number for Social Security.²

The BCR data were restricted to patients aged 50-75 years old, reflecting the NELSON population. This resulted in a population of 27 421 patients. Most patients were male (17 209 men (62.8%) and 10 212 women (37.2%)). Figure 19 presents the observed survival probability for lung cancers patients per stage and histology (NSCLC and SCLC).

Figure 19 – Observed survival probability per stage and histology



NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.



The above survival curves are used in the economic model. Adopting a lifetime time horizon is necessary to capture the full possible impact on all relevant incremental costs and effects. Therefore, the survival curves are extrapolated in the future. In the NELSON trial, the median age of cancer diagnosis was 61 years. We apply the age of 60 years at the beginning of our model. With the second screening round one year later, the median age of cancer diagnosis also becomes 61 years in our model. At the end of the observed survival curves, the mortality risk increases with the absolute increase in mortality risk of the general Belgian population of the same age and with the same sex distribution. As shown in Figure 20 – part a, blindly applying this approach did not provide reliable results. In the longer term, less data are available and the shape of the survival curve is less stable. The shape of the curve in the last period also determines the shape in the extrapolation period. Without any correction, the survival curves of stage I,

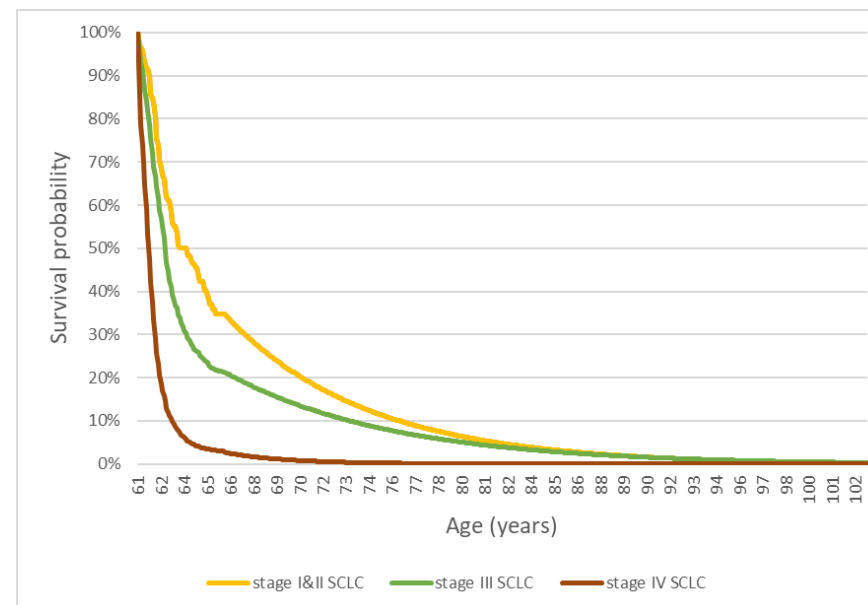
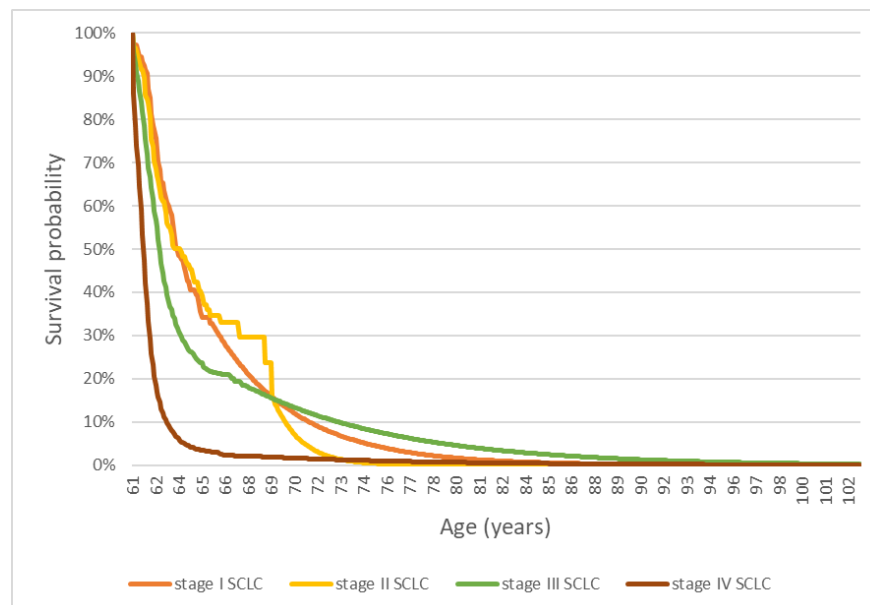
II and III small cell lung cancers cross, which is not realistic. Based on the curves presented in Figure 19, we decided to combine the survival curves for stage I and II SCLC. Furthermore, the observed survival curves were cut-off in a period when the mortality risk was rather stable. For NSCLC, we took a period of seven years, while for SCLC a period of five years was taken. The result is shown in Figure 20 – part b, and shows non-crossing survival curves for SCLC which are used in the economic model. Figure 21 shows the observed survival curves and extrapolations for NSCLC which are used in the economic model.

The number of life years gained is calculated by applying the survival probability for NSCLC and SCLC according to stage in both the intervention and control arm.

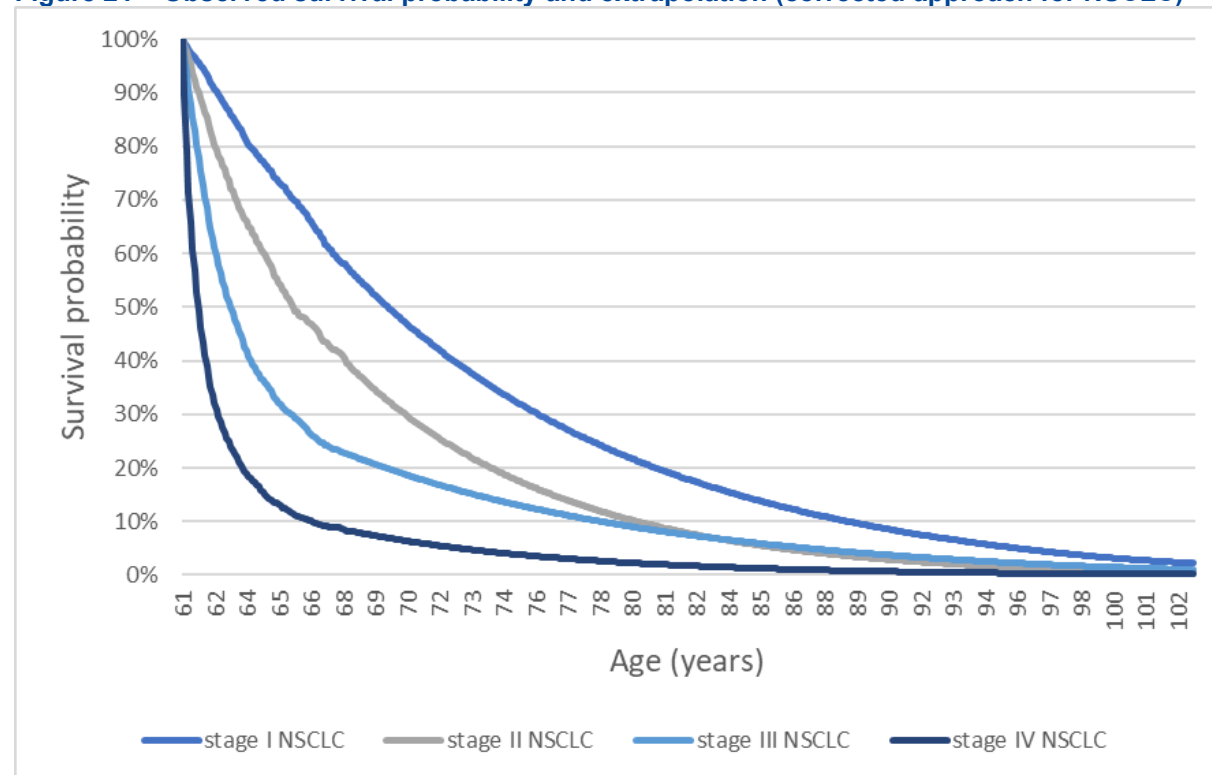


Figure 20 – Observed survival probability and extrapolation (uncorrected and corrected approach for SCLC)

A. Uncorrected extrapolation of survival curves for SCLC (not used in the economic model) **B. Corrected extrapolation of survival curves**



SCLC: small cell lung cancer.

**Figure 21 – Observed survival probability and extrapolation (corrected approach for NSCLC)**

NSCLC: non-small cell lung cancer.



6.1.7.9. Utilities

An overview of the input variables related to quality of life is presented in Table 59.

Table 59 – Overview of input variables related to quality of life

Variable	Value	Uncertainty	Source
Lung cancer (utilities)			
• Base case:			
• Stage I	0.81 (SD: 0.17)	Beta (3.50; 0.82)	Tramontano et al. ¹⁹⁶
• Stage II	0.77 (SD: 0.17)	Utility stage II = utility stage I - 0.04	
• Stage III	0.77 (SD: 0.18)	Utility stage III = utility stage II	
• Stage IV	0.76 (SD: 0.19)	Utility stage IV = utility stage I - 0.05	
• Scenario:		Scenario 'utilities'	
• Stage I-II	0.78 (95% CI: 0.70 – 0.86)	Beta (79.6; 22.4)	Blom et al. ²⁰⁸
• Stage III-IV	0.69 (95% CI: 0.65 – 0.73)	Beta (353.7; 158.9) + correlation with stage I-II utilities to avoid illogical values	
QoL loss (disutilities)			
• Base case:			
• Indeterminate findings	-0.0307 for 3 months	Beta (mean:0.0307; min: 0.018; max: 0.041)	Van den Bergh et al. ⁶⁸
• False positive findings			
• Scenario:	-0.063 for 3 months	Scenario 'disutility': -0.063 (fixed)	Mazzone et al. ²¹⁹

SD: standard deviation.

Lung cancer screening can have both positive and negative effects on quality of life. On the positive side, we have the improvement in quality of life if lung cancer is diagnosed at an earlier stage. Assigning lower utilities to more advanced lung cancers (i.e., higher stages), combined with the modelled stage shift and stage-dependent mortality, results in an estimate of the number of QALYs for the intervention and comparator group. On the negative side, we have, for example, the impact due to indeterminate or false positive results. We included both the positive and the negative impact on QoL in the economic model.

For information on QoL, we relied on several sources: 1) results from a targeted (non-systematic) search strategy in which we looked for reviews regarding quality of life in lung cancer patients; 2) the impact on quality of life as presented in the NELSON trial; and 3) QoL information identified in the economic literature review.

For the targeted (non-systematic) search strategy, we searched for systematic reviews on Pubmed and Google Scholar using the terms 'quality of life' and 'lung cancer'. The following articles were identified:



- Jovanoski et al. Health State Utility Values in Early-Stage Non-small Cell Lung Cancer: A Systematic Literature Review. *Pharmacoecon Open*. 2023 Sep;7(5):723-738.²⁴²
 - No suitable information identified: advanced/metastatic (stage IV) NSCLC was explicitly excluded, while this is a relevant health state in our economic model.
- Pourrahmat et al. Health state utility values by cancer stage: a systematic literature review. *Eur J Health Econ*. 2021 Nov;22(8):1275-1288.²⁴³
 - Two included studies present QoL differences between stage IV and stage I, II or III lung cancer: Tramontano et al.¹⁹⁶ and Kim et al.²⁰⁴
- Blom et al. Systematic Review and Meta-Analysis of Community- and Choice-Based Health State Utility Values for Lung Cancer. *Pharmacoeconomics*. 2020 Nov;38(11):1187-1200.²⁰⁸
 - Meta-analysis of (heterogeneous) studies reporting utility values for lung cancer by stage.
- Paracha et al. Systematic review of health state utility values in metastatic non-small cell lung cancer with a focus on previously treated patients. *Health Qual Life Outcomes*. 2018 Sep 12;16(1):179.²⁰²
 - No suitable information identified since no utility values are presented for all relevant health states (i.e. stages) in our model.
- Sturza J. A Review and Meta-Analysis of Utility Values for Lung Cancer. *Medical Decision Making*. 2010;30(6):685-93.²¹⁰
 - No suitable information identified since no utility values are presented for all relevant health states (i.e., stages) in our model.
- meet eligibility criteria for lung cancer screening. *Lung Cancer*. 2022;169:47-54.¹⁹⁹
- Jang RW, Isogai PK, Mittmann N, Bradbury PA, Shepherd FA, Feld R, et al. Derivation of Utility Values from European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire Values in Lung Cancer. *Journal of Thoracic Oncology*. 2010;5(12):1953-7.²⁰⁰
- Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health and Quality of Life Outcomes*. 2008;6(1):84.²⁰³
- Grutters JPC, Joore MA, Wiegman EM, Langendijk JA, Ruyscher Dd, Hochstenbag M, et al. Health-related quality of life in patients surviving non-small cell lung cancer. *Thorax*. 2010;65(10):903-7.²⁴⁴
- Trippoli S, Vaiani M, Lucioni C, Messori A, Quality-of-life Study Group of the Master 2 Project in P. Quality of Life and Utility in Patients with Non-Small Cell Lung Cancer. *Pharmacoeconomics*. 2001;19(8):855-63.²⁰⁵

None of the references listed above presented utility values for the health states relevant to our model, i.e., stage I, II, III and IV lung cancers. The study by Kim et al.²⁰⁴ was also excluded as it was a study in which six hypothetical health states for lung cancer were converted to utility values via a standard-gamble exercise in a Korean population without lung cancer. Preference is given to studies in which the health state is assessed by patients with lung cancer.

As the most relevant and applicable study, the analysis of Tramontano et al.¹⁹⁶ was selected:

The following potentially relevant references were additionally identified through the literature review of economic evaluations:

- Ngo PJ, Wade S, Vaneckova P, Behar Harpaz S, Caruana M, Cressman S, et al. Health utilities for participants in a population-based sample who

- Tramontano et al. Catalog and comparison of societal preferences (utilities) for lung cancer health states: results from the Cancer Care Outcomes Research and Surveillance (CanCORS) study. *Med Decis Making*. 2015 Apr;35(3):371-87.



Utilities for stage I, II, III and IV lung cancer

In the US-based study of Tramontano et al.,¹⁹⁶ CanCORS investigated the quality of cancer care and patient outcomes. Beginning in September of 2003, a cohort of 5,015 patients with newly diagnosed lung cancer was recruited from patients receiving care at one of the participating health care systems. The EQ-5D health states were measured in patients shortly after lung cancer diagnosis and 11-13 months after diagnosis. For the baseline survey, the analysis was restricted to the 2396 patients who were alive and completed the full baseline interview themselves and had no missing data. For the follow-up survey, information from 1474 patients who participated in a follow-up survey approximately one year after diagnosis was included to explore the change in EQ-5D scores over time. The utilities were derived from the health states by applying a time-trade off US population-based algorithm provided by AHRQ.

At baseline, the mean utility values for the different stages of lung cancer were as follows: stage I: 0.81 (SD 0.17); stage II: 0.77 (SD 0.17); stage III: 0.77 (SD 0.18); and stage IV: 0.76 (SD 0.19). At follow-up this was: stage I: 0.82 (SD 0.17); stage II: 0.80 (SD 0.17); stage III: 0.79 (SD 0.19); and stage IV: 0.77 (SD 0.19). The incremental difference in utilities of 0.05 between stage I and stage IV lung cancers remained the same. Therefore, we decided to apply the baseline utility values in the economic model in which lower utility values were modelled for stage II, III and IV lung cancers in comparison with stage I lung cancers (see Table 59).

An advantage of the CanCORS cohort is the large size and standardized data collection, including the EQ-5D. The presented utilities are also stage-specific and present all stages at diagnosis as included in our economic model. A disadvantage is that the EQ-5D-3L version was used, including three levels for the five dimensions. The newer version of the EQ-5D with five levels for each dimension (EQ-5D-5L) is less affected by a ceiling effect and could provide different utility values. Furthermore, as stated by the authors, patients who were too ill to complete a detailed survey were not included. As a result, mean utilities might have been underestimated the full impact of advanced disease.¹⁹⁶

As an alternative scenario, the utilities from the meta-analysis of Blom et al.²⁰⁸ were included in the economic model: stage I-II: 0.78 (95% CI 0.70 – 0.86); stage III-IV: 0.69 (95% CI 0.65 – 0.73). A major limitation of the study of Blom et al.²⁰⁸ is that different studies with a large heterogeneity are combined, which can lead to strange results: the average utility of the 'all stages' category of 0.68 is lower than the average utility of 0.78 for stage I-II or 0.69 for stage III-IV lung cancers. The pooled value for all stages was based on data from 5100 individuals. For stage I-II and stage III-IV estimates, this were 1510 and 4703 individuals, respectively.²⁰⁸ Combining utilities from different studies causes methodological problems. Nevertheless, we decided to include the utility values of this study to see the impact on the ICERs if a larger difference in utilities between stage I and IV is applied (Scenario 'utilities').

Disutilities for indeterminate and false positive results

In the clinical part of this report, it was mentioned that the limited evidence available from LDCT trials does not suggest any long-term adverse impact on HRQoL with LDCT screening. In a subset of the NELSON participants, indeterminate results lead to short-term increases in distress which had resolved at 2-year follow-up.⁶⁸

The NELSON-based study of van den Bergh et al.⁶⁸ showed that lung-cancer-specific distress increased in a clinically relevant manner 2 months after receipt of an indeterminate result of baseline screening. After receiving the baseline CT result, subjects with an indeterminate screening result had clinically relevant higher lung-cancer-specific distress than subjects with a negative result. In the study, QoL was measured at four time points: T0: before randomization; T1: 1 week before baseline screening; T2: 1 day after the screening; and T3: 2 months after the screening results but before the 3-month follow-up CT. At T0, T1, and T2 no statistically significant differences were found in EQ-5D-VAS and STAI-6 (the Spielberger State-Trait Anxiety Inventory) scores between subjects with a negative and an indeterminate test result.⁶⁸ At T3, compared with subjects with a negative result, those with an indeterminate result had statistically significantly lower scores on the EQ-5D-VAS and higher scores on the STAI-6 (i.e., both worse), but the difference was not clinically relevant although statistically



significant (both P 's <0.01).⁶⁸ In the participants with a negative CT scan result, the mean EQ-5D VAS scores were 79.4, 78.7, and 79.4 at T0, T1 and T2, respectively, or an average of 79.2. This is exactly the same as the score at T3. In the participants with an indeterminate CT scan result, the mean EQ-5D VAS scores were 79.1, 76.8 and 78.3 at T0, T1 and T2, respectively, or an average of 78.07. At T3, the EQ-5D VAS score was 75.0. This difference of 3.07 on the VAS scale was included as a disutility of -0.0307 in our model. The authors state that an indeterminate test result had at least some negative impact on HRQoL in the period between receipt of the test result and the follow-up scan 3–4 months later. In our model, the disutility is included for a period of 3 months. The disutility is applied for both indeterminate and false positive results. Both disutilities are included in our base case, given this evidence is based on information from the NELSON trial.

In the economic evaluation of Griffin et al.¹³⁹ and the UK NSC study¹¹⁶ a scenario including a disutility of 0.063 for 3 months²¹⁹ was included for false positive results. This disutility is modelled in a scenario analysis, for both false positive and indeterminate results. In addition, a separate scenario analysis is conducted where this disutility is omitted (Scenario 'disutility').

Other (dis)utilities

There may be a (limited) loss of quality of life due to participation in LCS for the period when participants are waiting for the screening result. In the study by Griffin et al.¹³⁹ and the UK NSC study,¹¹⁶ a disutility of 0.01 is assumed for 2 weeks. In our model, we assume no disutility for voluntary participation in lung cancer screening.

No QoL information was identified related to the loss of QoL due to overdiagnosis. Some argue that people with an overdiagnosed stage I lung cancer might not have a major loss in QoL because these people are 'relieved' lung cancer was detected so early and they thank their lives due to the early screening (expert opinion). On the other hand, there is still the impact on QoL due to the 'unnecessary' treatment and because these people are faced with the (unnecessary) diagnosis of cancer. Due to the lack of evidence, no disutility was modelled. Also for the lead time, no disutility was modelled. Not including a potential loss of quality of life for

overdiagnosis and/or lead time means that we may be modelling optimistically for quality of life. On the other hand, if the difference in quality of life between e.g., stage I and IV lung cancer is larger than observed in the study by Tramontano et al.,¹⁹⁶ this would result in an underestimation of the potential gain in QALYs. The combined impact of this potential under- and overestimation is difficult to estimate.

6.1.7.10. Diagnosis and treatment costs

For costs related to diagnosis and treatment, we refer to the analysis of Belgian costs in Chapter 0. The costs are shown for five different categories: diagnosis, radiotherapy, surgery, systemic therapy, and palliative care. Finally, we also add theoretical follow-up costs.

For costs in the first year after lung cancer diagnosis, we use the cost information for patients aged 50-74 years with a lung cancer diagnosed in 2020. Thus, we use the most recent data available. For the costs after the first year in the model, we cannot use the cost data of the most recent year as no longer-term cost information is available yet for these patients. Therefore, for the cost information after the first year, we use the data available for all patients aged 50-74 years with a lung cancer diagnosed between 2015 and 2020 (see data selection in part 5.2.2). Costs are shown per stage and histology. Please refer to part 6.1.8 for the uncertainty surrounding these costs.

Half-cycle correction and the duration of the time period

To calculate the average cost, it is necessary to calculate the total cost over a period of time and divide it by the number of patients in the sample. However, the number of patients in the sample decreases over time due to mortality. It is not correct to take as denominator the number of patients at the beginning or the end of the period. A solution to this is to apply the half-cycle correction. Here, we take as denominator the number of patients halfway through the time period. When applying this approach, it is important to check whether the length of the period is not too long (or unnecessarily short), i.e., whether the number of patients in the sample halfway is approximately equal to the average of the number of patients at the beginning and end of the period. Because of high mortality (e.g., in stage IV



lung cancer), this is not the case with a one-year period for the first year. By shortening the period to 1 month for the first 3 months, and then 3 months for the remaining 9 months of the first year, the average cost per time unit could however be calculated correctly using the half-cycle approach. For the costs of the 2nd to 5th year, a time period of one year was appropriate (because the number of patients present at the half of the cycle was about the same as the average of the number of patients at the beginning and end of the period). Average costs are thus shown for the following 10 time periods: 1st month, 2nd month, 3rd month, months 4-6, months 7-9, months 10-12, year 2, year 3, year 4 and year 5. For costs after the 5th year, we assume they are equal to the costs reported for the 5th year.

Year of costing

Where possible, we have used the latest cost information. Billing codes from Nomensoft were included for the year 2024. First-year cost data for patients diagnosed with cancer in 2020 include costs for the year 2020-2021. For the 2nd-5th year, cost data from 2015 to 30 June 2022 are included (i.e., the last date up to which IMA - AIM data linked to BCR data were available). We

chose not to make an adjustment via indexation as the individual year-by-year data showed that costs for the different categories do not systematically increase throughout the years (see, for example, diagnostic and staging costs or surgery costs in part 5.3.2).

In- and excluding supplements

As stated before (see part 6.1.4) and in accordance with the Belgian guidelines for economic evaluations,²²⁷ payments out of the government's health care budget as well as patients' co-payments are included. In the base case, supplements are excluded. In a scenario analysis, patients' supplements are also included (Scenario 'supplements').

Diagnostic and staging costs

Table 60 and Table 61 present the diagnostic and staging costs, excluding and including supplements, respectively. As expected, most costs for this category are identified in the month before or after the date of the diagnosis.

Table 60 – Diagnostic and staging costs, excluding supplements (per time period, stage and histology)

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
Pre-period	€692	€935	€748	€1047	€626	€529	€514	€450
1st month	€822	€836	€1036	€1002	€1165	€1113	€1200	€1015
2nd month	€223	€274	€252	€122	€231	€144	€195	€159
3rd month	€137	€179	€169	€120	€220	€165	€185	€192

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.


Table 61 – Diagnostic and staging costs, including supplements (per time period, stage and histology)

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
Pre-period	€725	€1055	€806	€1051	€659	€545	€548	€473
1st month	€920	€916	€1177	€1032	€1237	€1187	€1291	€1089
2nd month	€269	€306	€288	€122	€267	€146	€209	€175
3rd month	€151	€185	€215	€120	€233	€183	€196	€205

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

Radiotherapy

Table 62 and Table 63 present the radiotherapy costs, excluding and including supplements, respectively.

Table 62 – Radiotherapy costs, excluding supplements (per time period, stage and histology)

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€117	€404	€114	€419	€218	€431	€892	€344
2nd month	€491	€1131	€236	€1156	€442	€1090	€515	€127
3rd month	€305	€582	€339	€735	€684	€1075	€194	€139
Month 4-6	€287	€1964	€421	€1490	€1397	€1957	€482	€837
Month 7-9	€116	€462	€138	€258	€426	€578	€457	€964
Month 10-12	€87	€730	€250	€0	€287	€222	€447	€508
Total 1st year	€1404	€5274	€1498	€4059	€3453	€5353	€2987	€2919
Year 2	€295	€631	€612	€698	€845	€1017	€1344	€2378
Year 3	€240	€357	€389	€441	€516	€502	€829	€1134
Year 4	€187	€333	€286	€277	€330	€205	€592	€468
Year 5	€155	€0	€233	€530	€209	€118	€475	€628

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

**Table 63 – Radiotherapy costs, including supplements (per time period, stage and histology)**

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€117	€404	€115	€419	€218	€439	€906	€344
2nd month	€491	€1131	€236	€1156	€448	€1093	€520	€127
3rd month	€307	€612	€353	€735	€689	€1084	€196	€139
Month 4-6	€293	€1989	€421	€1490	€1402	€1964	€482	€837
Month 7-9	€117	€462	€138	€258	€437	€578	€457	€978
Month 10-12	€87	€730	€250	€0	€292	€222	€460	€508
Total 1st year	€1412	€5330	€1513	€4059	€3486	€5379	€3022	€2933
Year 2	€301	€631	€619	€698	€859	€1026	€1360	€2404
Year 3	€243	€357	€395	€441	€522	€528	€831	€1164
Year 4	€188	€333	€286	€277	€336	€205	€605	€468
Year 5	€158	€0	€233	€530	€211	€118	€476	€628

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.



Surgery

Table 64 and Table 65 present the surgery costs, excluding and including supplements, respectively.

Table 64 – Surgery costs, excluding supplements (per time period, stage and histology)

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€3756	€5275	€4407	€1848	€869	€0	€207	€0
2nd month	€1894	€1790	€1964	€538	€1014	€56	€108	€0
3rd month	€595	€1596	€1178	€0	€391	€0	€60	€12
Month 4-6	€860	€1049	€1106	€257	€594	€0	€129	€0
Month 7-9	€281	€0	€0	€0	€60	€90	€34	€0
Month 10-12	€49	€0	€26	€0	€41	€0	€14	€0
Total 1st year	€7435	€9710	€8682	€2642	€2969	€146	€551	€12
Year 2	€164	€566	€137	€789	€162	€26	€74	€41
Year 3	€113	€183	€93	€318	€85	€124	€40	€0
Year 4	€104	€0	€53	€0	€70	€172	€50	€0
Year 5	€42	€0	€18	€0	€27	€0	€49	€0

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

**Table 65 – Surgery costs, including supplements (per time period, stage and histology)**

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€4281	€5377	€5031	€1883	€991	€0	€239	€0
2nd month	€2223	€1834	€2184	€543	€1174	€57	€120	€0
3rd month	€643	€1610	€1414	€0	€429	€0	€62	€13
Month 4-6	€933	€1368	€1201	€260	€674	€0	€143	€0
Month 7-9	€309	€0	€0	€0	€61	€90	€35	€0
Month 10-12	€62	€0	€27	€0	€42	€0	€14	€0
Total 1st year	€8451	€10 190	€9857	€2686	€3371	€148	€614	€13
Year 2	€183	€573	€151	€871	€193	€34	€89	€42
Year 3	€125	€183	€114	€423	€93	€127	€53	€0
Year 4	€128	€0	€67	€0	€89	€180	€59	€0
Year 5	€51	€0	€19	€0	€33	€0	€51	€0

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

Systemic therapy

Table 66 and Table 67 present the systemic therapy costs, excluding and including supplements, respectively.

We remark that the cost of this systemic therapy does not reflect the true cost. Most of the expensive therapies are reimbursed under a so-called managed entry agreement. In such an agreement, a confidential price discount is agreed upon between the company and the government. The cost information from the IMA - AIM database does not take into account these confidential discounts. According to the Belgian MORSE (Monitoring of Reimbursement Significant Expenses) report,²⁴⁵ this discount averaged 53.8% in 2022. This was as follows in previous years: 12.2% (2015), 18.6% (2016), 25.5% (2017), 27.2% (2018), 39.4% (2019) and 40.4% (2020).

Not including a price discount in the base case would be incorrect as it is a certainty that discounts are applied. The costs for the first year are based on the data for patients with a lung cancer diagnosis in 2020 (and therefore spending in 2020 or 2021). The average discount could easily be higher or lower than the previously mentioned 40.4% or 53.8% discount. While the largest part of the systemic therapy costs are related to immunotherapy and targeted therapies drugs (see Figure 16 in part 5.3.2.2), not all products in our sample are drugs reimbursed under a managed entry agreement. On the other hand, the price discount of individual products could easily be much higher/lower than the published average. Since we do not know the size of this discount, we work with different scenarios. In the base case, we decided to apply a 40% discount to the total systemic therapy cost. In scenario analyses, this price discount varies in 10% increments from no discount to a 90% discount (Scenario 'price discount').


Table 66 – Systemic therapy costs, excluding supplements (per time period, stage and histology)

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€96	€122	€201	€837	€1152	€1275	€4134	€5444
2nd month	€175	€600	€844	€1585	€2111	€1602	€8016	€6734
3rd month	€234	€479	€1208	€1172	€2548	€1777	€9069	€6787
Month 4-6	€493	€1121	€2463	€2142	€9552	€2657	€23173	€16734
Month 7-9	€598	€4120	€1772	€1679	€10858	€2021	€20017	€10533
Month 10-12	€842	€4624	€1910	€3481	€11340	€2658	€17808	€9322
Total 1st year	€2437	€11 066	€8398	€10 898	€37 560	€11 990	€82 217	€55 554
Year 2	€2696	€3836	€8403	€7691	€22 991	€9021	€48 791	€21 814
Year 3	€2922	€2644	€8322	€8639	€15 435	€4932	€35 272	€17 638
Year 4	€3163	€2551	€7941	€6211	€12 479	€3674	€27 258	€9241
Year 5	€2850	€0	€6540	€731	€11 670	€2979	€20 577	€3748

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

**Table 67 – Systemic therapy costs, including supplements (per time period, stage and histology)**

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€96	€124	€204	€843	€1162	€1328	€4143	€5480
2nd month	€176	€689	€854	€1627	€2134	€1645	€8028	€6768
3rd month	€236	€530	€1218	€1201	€2571	€1822	€9079	€6819
Month 4-6	€495	€1124	€2478	€2143	€9570	€2674	€23197	€16793
Month 7-9	€599	€4213	€1773	€1680	€10866	€2027	€20037	€10550
Month 10-12	€843	€4699	€1911	€3482	€11352	€2667	€17827	€9346
Total 1st year	€2445	€11 379	€8437	€10 975	€37 654	€12 163	€82 311	€55 756
Year 2	€2704	€3859	€8421	€7705	€23 028	€9071	€48 868	€21 915
Year 3	€2927	€2647	€8333	€8664	€15 464	€4969	€35 331	€17 705
Year 4	€3168	€2556	€7954	€6244	€12 506	€3696	€27 292	€9250
Year 5	€2855	€0	€6547	€731	€11 688	€2981	€20 605	€3750

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.



Palliative care

Table 68 and Table 69 present the palliative care costs, excluding and including supplements, respectively.

Table 68 – Palliative care costs, excluding supplements (per time period, stage and histology)

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€4	€0	€16	€43	€25	€30	€127	€157
2nd month	€8	€0	€17	€0	€46	€104	€174	€208
3rd month	€3	€0	€24	€0	€46	€81	€203	€182
Month 4-6	€8	€0	€105	€0	€142	€215	€495	€609
Month 7-9	€22	€0	€81	€0	€170	€207	€519	€783
Month 10-12	€31	€71	€96	€0	€183	€272	€443	€720
Total 1st year	€76	€71	€339	€43	€611	€909	€1962	€2659
Year 2	€233	€1376	€475	€1202	€862	€1407	€1546	€3187
Year 3	€247	€611	€419	€1102	€650	€944	€1105	€1806
Year 4	€212	€101	€495	€644	€570	€596	€1016	€1003
Year 5	€275	€43	€325	€775	€392	€268	€728	€469

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

**Table 69 – Palliative care costs, including supplements (per time period, stage and histology)**

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€4	€0	€16	€43	€25	€30	€127	€157
2nd month	€8	€0	€17	€0	€46	€104	€174	€208
3rd month	€3	€0	€24	€0	€46	€81	€203	€182
Month 4-6	€8	€0	€105	€0	€142	€215	€496	€609
Month 7-9	€22	€0	€81	€0	€170	€207	€519	€783
Month 10-12	€31	€71	€96	€0	€183	€272	€444	€721
Total 1st year	€76	€71	€339	€43	€611	€909	€1962	€2660
Year 2	€233	€1377	€475	€1202	€862	€1408	€1547	€3193
Year 3	€247	€611	€419	€1102	€650	€944	€1105	€1806
Year 4	€212	€101	€495	€644	€570	€596	€1016	€1003
Year 5	€275	€43	€325	€775	€392	€268	€728	€469

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

Uncertainty surrounding diagnosis and treatment costs

The uncertainty surrounding all costs included in Table 60 up to Table 69 is modelled as a normal distribution with the mean as presented and the 95% CI as a decrease/increase of the mean with 20%. We refer to part 6.1.8.1 for more details on this approach.

Summary table of diagnosis, radiotherapy, surgery, systemic therapy and palliative care costs

In Table 70 and Table 71, the average costs mentioned in the previous tables are summed up. We remark that the diagnostic costs from the pre-period are included in the first month. The total costs are higher for stage IV cancers in comparison with the other stages of lung cancer.



Table 70 – Total costs (diagnosis, radiotherapy, surgery, systemic therapy and palliative care), excluding supplements (per time period, stage and histology)

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€5488	€7572	€6522	€5196	€4055	€3379	€7075	€7409
2nd month	€2791	€3795	€3315	€3402	€3843	€2996	€9007	€7229
3rd month	€1273	€2836	€2918	€2027	€3887	€3097	€9710	€7312
Month 4-6	€1648	€4135	€4095	€3889	€11 685	€4829	€24 279	€18 180
Month 7-9	€1017	€4583	€1990	€1938	€11 514	€2896	€21 026	€12 281
Month 10-12	€1008	€5426	€2282	€3481	€11 850	€3151	€18 713	€10 550
Total 1st year	€11 352	€26 122	€18 917	€17 642	€44 593	€18 398	€87 717	€61 145
Year 2	€3389	€6409	€9627	€10 380	€24 859	€11 472	€51 756	€27 420
Year 3	€3522	€3795	€9222	€10 500	€16 687	€6501	€37 246	€20 577
Year 4	€3666	€2985	€8775	€7133	€13 449	€4648	€28 916	€10 712
Year 5	€3323	€43	€7116	€2036	€12 298	€3365	€21 829	€4845

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.



Table 71 – Total costs (diagnosis, radiotherapy, surgery, systemic therapy and palliative care), including supplements (per time period, stage and histology)

Period	Stage I		Stage II		Stage III		Stage IV	
	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC	NSCLC	SCLC
1st month	€6144	€7877	€7349	€5270	€4292	€3529	€7254	€7542
2nd month	€3167	€3961	€3579	€3449	€4069	€3045	€9051	€7278
3rd month	€1339	€2937	€3223	€2056	€3967	€3170	€9737	€7357
Month 4-6	€1730	€4481	€4205	€3894	€11 788	€4853	€24 317	€18 239
Month 7-9	€1047	€4675	€1992	€1938	€11 534	€2904	€21 048	€12 311
Month 10-12	€1023	€5501	€2284	€3482	€11 869	€3160	€18 745	€10 575
Total 1st year	€12 385	€26 969	€20 146	€17 764	€45 122	€18 600	€87 909	€61 362
Year 2	€3422	€6440	€9667	€10 475	€24 942	€11 540	€51 864	€27 554
Year 3	€3541	€3798	€9261	€10 631	€16 729	€6568	€37 320	€20 674
Year 4	€3696	€2990	€8802	€7165	€13 502	€4677	€28 972	€10 721
Year 5	€3339	€43	€7124	€2037	€12 323	€3367	€21 860	€4847

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

Follow-up

A theoretical assumption was formulated regarding the follow-up after lung cancer treatment, as specialist visits are not represented in our Belgian database and given the non-specific nature of follow-up examinations such as chest X-rays and thoracic CT scans. Considering the European Society for Medical Oncology (ESMO)²⁴⁶ and American Society of Clinical Oncology (ASCO)²⁴⁷ guidelines and expert input, the follow-up was established to include a contrast-enhanced thoracic CT scan and a pulmonologist visit and we assumed it to be as follows:

- For stage I-III lung cancers (NSCLC/SCLC): every 6 months for 2 years, then annually

- For stage IV lung cancers (NSCLC/SCLC): every 3 months for 2 years, then every 6 months for 2 years, then annually

The cost for this follow-up scan is €330.57 (€278.13 + €52.44). In our model, the initial follow-up examination occurs six months after the lung cancer incidence to prevent duplicate counting of diagnostic tests.

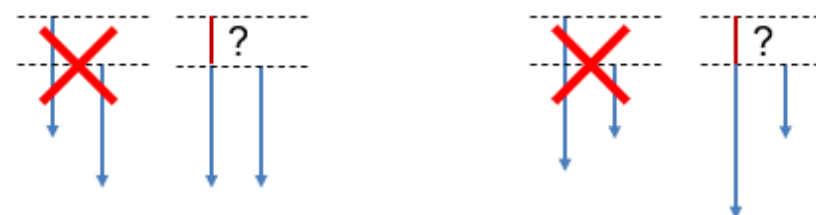
6.1.7.11. Lead time

Due to the lead time, survival time of people diagnosed from screening will appear longer due to the early detection, even if the earlier detection has no effect on the course of the disease or the actual time of death (see part 2.2.4). Including the lead time poses challenges for the model. Based on the Belgian data, we have survival information for lung cancer patients in which cancer was diagnosed between the age of 50 and 75 years, according to stage and histology. These are survival probabilities for patients diagnosed with lung cancer outside a lung cancer screening programme.

It is not correct to simply shift the start of diagnosis in time in the intervention or comparator group as assigning the same survival data for a cancer with the same stage would then result in a different survival (see Figure 22, left side of both panels). Alternatively, we keep the same survival for a cancer with the same stage and histology and assign an increased discount rate in the comparator group (reflecting the cost would occur further in the future). The formula for discounting is usually the following: $\text{value} / (1 + \text{discount rate})^{\text{time}}$. In this case, the length of the lead time is added to the time for applying the discount rate: $\text{value} / (1 + \text{discount rate})^{\text{time} + \text{lead time}}$. This approach can also be applied if there is a stage shift (Figure 22, right panel). This simplified approach has the advantage that the number of modelled cancers remains exactly the same as in the previous analyses - thus continuing to reflect the evidence on which we rely.

Figure 22 – Incorrect and simplified method of including lead time in the model (exploratory analysis)

Diagnosis of cancers with the same stage diagnosis of cancers with a different stage (stage shift)



Blue line: length of survival; start point of the line: diagnosis of the cancer; red line: length of the lead time. Left side: incorrect method; right side: simplified approach (adding the lead time in the formula of the discount rate).

In the identified economic evaluations, only three studies varied the lead time, using lead times between 0.5 and 2 years (see Section 4.3.2). Bebossat²⁴⁸ performed a non-systematic search of the literature for estimates of the lead time and screening trials. The lead time is defined as the time interval from detection of lung cancer by screening to the development of symptoms. Lead time since detection by LDCT was 1.1-3.5 years if derived from prevalence/incidence ratios and 3.9 years if derived from tumour doubling time (for details we refer to the original publication). In the base case, we don't include a lead time. In an exploratory analysis, we include a lead time of 1, 2, 3 or 4 years (Scenario 'lead time').

6.1.7.12. Smoking cessation, incidental findings and radiation exposure

In the NELSON trial, at randomization, all current smokers in both study arms received a standard smoking cessation brochure or a questionnaire by which people could ask for tailored smoking cessation information from STIVORO, the Dutch expert centre on tobacco control.²⁴⁹ Van der Aalst et al.²⁴⁹ investigated the smoking behaviour in two random samples of male



smokers in the screen (n=641) and control arm (n=643) before (T0) and 2 years after randomisation (T1). Almost 17% (16.6%) of the trial participants quit smoking, which was indicated to be higher than the 3-7% found in the general adult population. This study showed that all trial participants stopped smoking more than expected, although tailored smoking cessation advice had no advantage over standard smoking cessation. In general, the study results suggest that screening is a teachable moment to improve smoking behaviour.

Since smoking cessation was offered in both the intervention and control arm of the NELSON trial it can be excluded as an incremental cost. However, in real life outside of an RCT, this extra teachable moment would not occur without lung cancer screening. As such, this provides an argument to see smoking cessation as an incremental cost. However, in this case, also the positive incremental effect of smoking cessation should be included. This cannot be done based on the NELSON trial in which both arms of the RCT receive the same smoking cessation intervention. Therefore, it was decided not to include the costs for smoking cessation in the economic evaluation. Nevertheless, if it is decided to introduce lung cancer screening, smoking cessation would be an essential component of this intervention since it improves the cost-effectiveness of lung cancer screening. We will return to this in the discussion.

In the clinical part of this report, an exploratory analysis was performed to estimate the prevalence of incidental findings for which an additional examination is recommended according to the ERS Statement. Our estimation suggests that approximately 23% of screening participants would require an additional examination for incidental findings (see part 3.2.10). The incremental costs for these incidental findings are not included since it is not possible to know the direction and magnitude of the incremental effects linked to these incidental findings. Concerning radiation exposure, the estimated radiation-related lifetime attributable risk to develop cancer was below 0.25% for women and about 0.1% for men (see part 3.2.11). Also here it is not clear what would be the magnitude of this impact. Therefore, the incremental impact related to radiation exposure is not included in the model. We come back to this in the discussion.

6.1.8. Uncertainty analysis

6.1.8.1. Probabilistic sensitivity analysis

Uncertainty surrounding the input variables was incorporated into the model by using probability distributions. The following probability distributions were chosen for the different variables:

- Beta distributions for the following probabilities:
 - Invitation to lung cancer screening: first response, eligible and invited, second response and inclusion in NELSON trial (see Table 43)
 - Screening uptake (1st, 2nd and 3rd round) and screening results: indeterminate and positive findings (1st, 2nd and 3rd round) (see Table 45)
 - Interval cancers (1st, 2nd and 3rd round) (see Table 47)
 - Diagnosis costs false positive findings: probability of receiving bronchoscopy, mediastinoscopy or lung surgery (see Table 47)
 - Overdiagnosis (see Table 57)
 - Utilities (see Table 59)
- Beta distribution with minimum and maximum limit:
 - Disutilities for indeterminate and false positive findings (see Table 59)
- Conditional beta distributions for the following probabilities:
 - True and false positive findings (1st, 2nd and 3rd round) (see Table 47)
 - Stages (I, II, III and IV) screen-detected cancers (1st, 2nd and 3rd round) (see Table 50)
 - Stages (I, II, III and IV) interval cancers (1st, 2nd and 3rd round) (see Table 50)



- Histology (NSCLC/SCLC) screen-detected cancers (1st, 2nd and 3rd round) (see Table 50)
- Histology (NSCLC/SCLC) interval cancers (2nd round) (see Table 50)
- Uniform distributions for the following cost items:
 - Costs related to screening campaign, invitation lung cancer screening, and communication screening results (see Table 43)
- Normal distribution:
 - Diagnosis and treatment costs based on the Belgian IMA – AMI data (see tables in part 6.1.7.10 and explanation hereafter).

Conditional beta distributions are chosen where probabilities must sum up to 100%. A uniform distribution is chosen for costs which are not based on a sample and where there is no information on the uncertainty surrounding these costs.

It is important to check whether logical values are modelled when applying probability distributions. For example, it is preferable for utilities to meet the following conditions: utility stage I $\geq$ utility stage II $\geq$ utility stage III $\geq$ utility stage IV. The study by Tramontano et al.¹⁹⁶ published the following utilities: stage I: 0.81 (SD 0.17); stage II 0.77 (SD 0.17); stage III 0.77 (SD 0.18) and stage IV 0.76 (SD 0.19). If the utilities for these stages are modelled as independent values by applying a beta distribution, the rationale of better utilities for all lower lung cancer stages is not respected in $\frac{3}{4}$ of the simulations. The reason is the combination of mean utilities that are close to each other (0.81, 0.77 and 0.76) in combination with a large SD. The occurrence of these illogical values is not desirable for population-level modelling. In this case, including a correlation was not sufficient to solve this problem. The solution adopted is to first model the utility for stage I lung cancer as a beta distribution applying the reported mean and standard deviation. Then, for the utilities for stages II, III and IV, the difference between the mean utility reported for the different stages is subtracted: i.e., minus 0.04 for stages II and III (i.e., 0.77 versus 0.81) and minus 0.05 for stage IV (i.e., 0.76 versus 0.81). For modelling utilities based on the study by Blom et al.,²⁰⁸ the problem was solved by applying a correlation between

the utilities drawn from the probability distributions for stage I-II and stage III-IV lung cancers. As such, no lower values are modelled in the 1000 simulations for a stage III-IV lung cancer compared to a stage I-II lung cancer.

Also for costs, we have to be careful not to model illogical values at the population level. It is possible, e.g., that an individual has no cost for radiotherapy or surgery. But it is not possible that for our total population the average cost would be zero. Thus, applying a probability distribution that yields correct values for individuals is not necessarily suitable for modelling at the population level. This is the case if we would apply a gamma distribution, which is nevertheless a widely used probability distribution for cost data. An alternative is to apply a normal distribution via the Central Limit Theorem. The Central Limit Theorem states that if sufficiently large samples are taken from a population, the means of these samples will be normally distributed even if the original sample is not normally distributed. When applying this Central Limit Theorem, and because of the wide standard deviation on the original cost data, the resulting normal distribution also had a wide confidence interval so that when applying 1000 simulations, negative values were also drawn from this distribution. This is obviously not a logical value for cost data. Hence, we opted to apply a normal distribution where the standard deviation was determined so that the 95% CI equals $\pm 20\%$ of the mean (formula: $((\text{mean} \times 1.2) - (\text{mean} \times 0.8)) / (1.96 \times 2)$). As such, we were able to reflect the correct mean costs extracted from the Belgian IMA – AIM data, as well as only simulating logical positive values for all our cost input variables.

The uncertainty surrounding the input variables is translated into the uncertainty about the incremental costs, incremental effects (per LYG or QALY gained), and ICERs (€/LYG or €/QALY gained). This is transparently reported by presenting the 95% CI for all these output variables in table format. The result of the base case analysis is also presented on the so-called cost-effectiveness plane and the cost-effectiveness acceptability curve.



6.1.8.2. Deterministic sensitivity analyses

Part 6.1.5 and 1.1.1 provided an explanation of the different variables for which a scenario analysis is performed. Table 72 provides an overview to make it more clear which values are chosen for the base case and how these are varied in scenario analyses. The results of these scenario analyses are presented both in table format and a tornado graph.

Table 72 – Overview variables in the base case analysis that are changed in scenario analyses

Variable	Base case	Scenario analysis	Source
Time horizon	10 years and lifetime time horizon	10, 20, 30, 40 and lifetime time horizon	See part 6.1.5
Discount rate	Costs: 3%; Effects: 1.5%	Scenario 'discount rate': - Costs and effects: 0% - Costs and effects: 3% - Costs and effects: 5%	See part 6.1.5
Invitation to lung cancer screening Second response & inclusion in NELSON (i.e., participation screening as a percentage of eligible and invited persons)	Beta (15 822; 15 137) (51.1%)	Scenario 'participation': 30%: Beta (9288; 21 671) 40%: Beta (12 384; 18 575) 60%: Beta (18 575; 12 384) 70%: Beta (21 671; 9288) 80%: Beta (24 767; 6192) 90%: Beta (27 863; 3096)	See part 6.1.7.1
Costs related to invitation for LCS - Invitation per letter (1st round) - Invitation 2nd or 3rd round	€0.5137 per invitation €0.393 per invitation	Scenario 'invitation cost': - Exclusion of this cost - Use of costs for Wallonia and Brussels: €0.65 for all three rounds.	See part 6.1.7.1
Other costs related to screening campaign Lump sum subsidy, periodic working group and awareness campaigns	€3.79 + €0.03 + €0.68 per invitation	Scenario 'invitation cost': Exclusion of this cost	See part 6.1.7.1



Costs communication screening results	Negative screening result: €0.209 per electronic result letter	Scenario 'communication cost': €1.2408 per result letter by post	See part 6.1.7.1
Screening uptake		Scenario 'adherence': 2 nd and 3 rd round: 50%	See part 6.1.7.2
• 1st round • 2nd round • 3rd round	Beta (7557; 342) (95.7%) Beta (7294; 462) (94.0%) Beta (6921; 644) (91.5%)		
Costs diagnosis false positive findings	Average cost of €2527 excluding supplements	Scenario 'supplements': average cost of €2752 including supplements	See part 6.1.7.3
Overdiagnosis	Beta (58; 185) (23.9%)	Scenario 'overdiagnosis': • Beta (18; 185) (8.9%) • Beta (40; 163) (19.7%) • Beta (5.35; 8.73) (38%)	See part 6.1.7.5
Quality of life: utilities lung cancer stages	Utilities according to Tramontano et al. ¹⁹⁶ • Stage I: 0.81 (SD 0.17) → Beta • Stage II: St. I – 0.04 • Stage III: St. I – 0.04 • Stage IV: St. I – 0.05	Scenario 'utilities': Utilities according to Blom et al. ²⁰⁸ • Stage I-II: 0.78 (95% CI 0.70 - 0.86) → Beta • Stage III-IV: 0.69 (95% CI 0.65 – 0.73) → Beta Remark: + correlation to avoid illogical values (see part 6.1.8.1)	See part 6.1.7.9
Quality of life: disutilities indeterminate and false positive findings	-0.0307 for 3 months → Beta	Scenario 'disutility': disutility excluded or -0.063 for 3 months (fixed)	See part 6.1.7.9
Diagnostic and treatment costs	Inclusion of costs for government and patients, exclusive supplements	Scenario 'supplements': inclusion of supplements	See part 6.1.7.10
Reduction total systemic therapy costs due to price discounts in managed entry agreements	On average 40%	Scenario 'price discount': 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% price discount	See part 6.1.7.10
Lead time	Base case: impact of lead time excluded	Scenario 'lead time': inclusion of a lead time of 1, 2, 3 or 4 years (only impact modelled on discount period for costs)	See part 6.1.7.11

LCS: lung cancer screening; SD: standard deviation; St.: stage.



6.1.9. Validation

When constructing an economic model, it is important to check that the model was constructed correctly and that no illogical or erroneous results are generated. It is also important to check whether the evidence used is reflected in the model. Therefore, several validations were performed:

- The formulas of the model were reviewed by a second health economist. The structure of the model was also co-reviewed by a third person with a clinical background.
- In addition to the incremental costs, incremental effects and ICERs, the output was also collected for a number of intermediate variables:
 - For the lung cancer screening group: the total number of cancers, the number of screen-detected cancers and the number of interval cancers; the percentage (and number) of overdiagnoses; the stage and histology distribution of screen-detected cancers in the 3 screening rounds.
 - For the control group: the total number of cancers; the stage distribution of these cancers.
- Modelling several variables at the same time and putting a lot of detail into a complex model can cause illogical values to emerge. In our model, the number of cancers is modelled according to both stage and histology. To model the number of cancers on which there is a positive impact via the stage shift, the number of overdiagnoses and the number of interval cancers are removed (see 6.1.7.7). It is possible that there are cells in the model where, in one of the 1000 simulations where a random number from the predefined probability distributions is drawn, the number of cancers in a given cell (e.g., stage IV SCLC in the control group) is smaller than the number of interval cancers in the lung cancer screening group. Subtracting this number would then lead to a negative number in the control group, which is not logical. To only obtain positive values, we checked in which simulations negative cells were present. This occurred only for SCLC cells. As a solution, in these cases, NSCLC of the same stage were transferred to the SCLC group to eliminate the negative number of cancers. This is only possible if a sufficient number of cancers was also present in the NSCLC group. Finally, we checked whether there were any simulations where negative cells remained after this modification and what the impact was on ICERs when removing these simulations. We note that this was done in addition to checking whether the number of stage I, II, III, IV was modelled correctly in both the intervention and control groups (see previous bullet).
- Finally, we also used an alternative way to calculate the number of life years gained and compare it with the number of life years gained calculated through the model. In the model, life years are gained via the stage shift. In the lung cancer screening group, there are more stage I cancers and fewer stage IV cancers compared to the control group. By linking these stages to the Belgian survival curves for the different lung cancer stages, the number of life years gained can be calculated. In an alternative approach, we calculated the number of life years gained by applying the hazard ratio to the KM survival curve of the comparator group, applying the following formula: $\text{probability of survival intervention} = \text{probability of survival control therapy}^{\wedge} (\text{hazard ratio})$. To apply this, we made a number of simplifications. In part 3.2.3, Bonney et al.⁵¹ reported a significant reduction of 5% in all-cause mortality (RR 0.95) with LDCT screening when combining trial data from eight available trials. In absence of a published hazard ratio from the meta-analysis, we used this relative risk as input for the hazard ratio and assumed it to be constant over time. We received the survival curve of the control group with 10 years of follow-up from the NELSON investigators. This way, we were able to calculate the potential number of life years gained after 10 years in an alternative way and compare it with the results of different scenarios applied in our model. To exclude the potential influence of the discount rate, this comparison was done without applying a discount rate for effects.



6.2. Results economic evaluation for Belgium

The NELSON trial had 7915 participants in the lung cancer screening arm. For ease of interpretation, we present results per 100 participants. This has no impact on the ICERs as a change in the number of participants has the same proportional impact on the numerator (incremental costs) and denominator (incremental effects).

We note that presented life years (and QALYs) in the lung cancer screening and comparator arm should not be interpreted as (quality-adjusted) life expectancy. The model excludes participants not diagnosed with lung cancer as there is no further incremental impact on costs or effects after obtaining the negative LDCT test result. As a result, the information on LYs (and QALYs) in the tables should not be interpreted as life years generated by all participants over a given time period. The numbers reflect the life years and QALYs of those who are incrementally impacted by lung cancer screening. This is a correct approach for calculating the ICERs where numerator and denominator reflect the incremental impact on costs and effects, respectively.

6.2.1. Time horizon

Applying a 10-year time horizon, the average ICER is almost €37 000 per QALY gained (Table 73). Applying a lifetime time horizon, this decreases to about €19 000 per QALY gained. As a reminder, this is the result for a scenario in which the participation and adherence reflects the information from the NELSON trial, an overdiagnosis of 23.87% is modelled, future costs are discounted at 3% and future effects at 1.5%, QoL is based on the study by Tramontano et al.,¹⁹⁶ and a price discount for systemic therapy of 40% is applied (for all base case inputs, see Table 72).

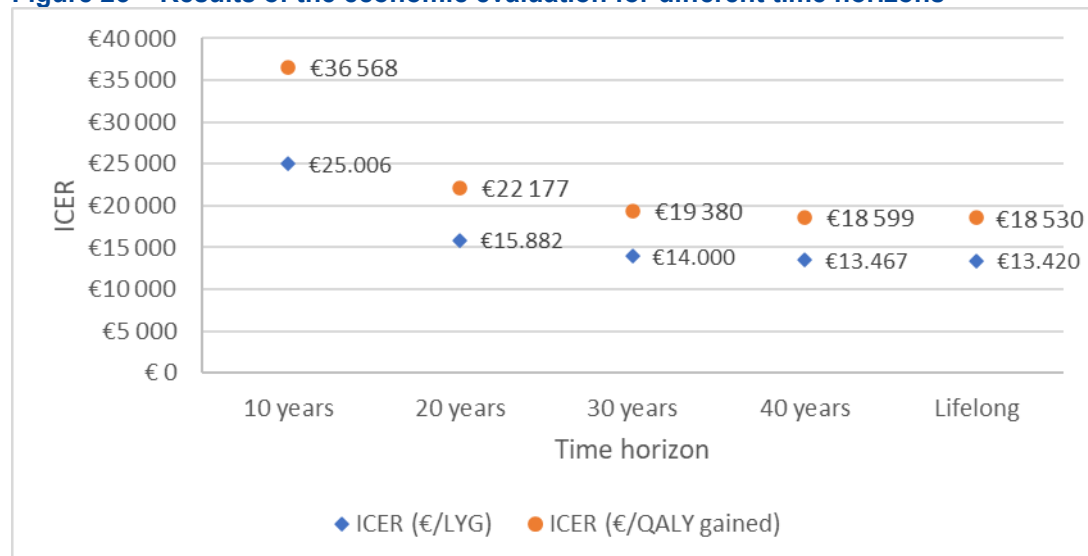


Table 73 – Results of the economic evaluation for different time horizons

Time horizon	Cost comparator	Cost intervention	Incremental cost	LYs comparator*	LYs intervention*	IE (LYG)	ICER (€/LYG)
				QALYs comparator*	QALYs intervention*	IE (QALYs gained)	ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
10 years	€87.305	€163.345	€76.040	5,91	9,03	3,12	€25.006
	(72.373 - 102.666)	(152.662 - 175.339)	(67.568 - 84.637)	(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(16.983 - 36.179)
				4,59 (2,16 - 6,29)	6,92 (3,24 - 9,56)	2,34 (1,00 - 3,49)	€36.568 (19.767 - 76.603)
20 years	€97.127	€174.139	€77.012	7,98	12,96	4,98	€15.882
	(80.540 - 114.139)	(162.135 - 187.828)	(68.260 - 85.659)	(6,64 - 9,41)	(10,75 - 15,37)	(3,68 - 6,41)	(10.924 - 22.679)
				6,21 (2,93 - 8,55)	10,06 (4,75 - 13,93)	3,85 (1,74 - 5,69)	€22.177 (12.383 - 44.620)
30 years	€99.983	€177.517	€77.534	8,70	14,38	5,69	€14.000
	(82.890 - 117.596)	(165.027 - 191.644)	(68.822 - 86.142)	(7,22 - 10,26)	(11,86 - 17,06)	(4,19 - 7,32)	(9.634 - 19.899)
				6,77 (3,20 - 9,30)	11,19 (5,29 - 15,52)	4,43 (2,03 - 6,52)	€19.380 (10.874 - 39.083)
40 years	€100.747	€178.475	€77.728	8,92	14,85	5,93	€13.467
	(83.560 - 118.520)	(165.925 - 192.698)	(69.021 - 86.330)	(7,41 - 10,53)	(12,22 - 17,61)	(4,37 - 7,62)	(9.267 - 19.107)
				6,94 (3,28 - 9,56)	11,56 (5,47 - 16,03)	4,62 (2,13 - 6,81)	€18.599 (10.449 - 37.482)
Lifelong	€100.808	€178.554	€77.747	8,94	14,89	5,95	€13.420
	(83.614 - 118.595)	(166.000 - 192.785)	(69.033 - 86.348)	(7,42 - 10,56)	(12,26 - 17,66)	(4,39 - 7,65)	(9.235 - 19.036)
				6,96 (3,29 - 9,58)	11,60 (5,49 - 16,07)	4,64 (2,14 - 6,83)	€18.530 (10.413 - 37.340)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

* remark: The reported LYs and QALYs are not the average life years or QALYs for the whole population in the lung cancer screening or comparator group. The model focusses on incremental elements and does not calculate life years or QALYs for participants not being confronted with lung cancer.

**Figure 23 – Results of the economic evaluation for different time horizons**

ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

6.2.2. Discount rate

Applying other discount rates for costs and effects has the expected impact on the ICER. The best results are obtained by not discounting (Table 74 and Table 75). Unequal discounting, as recommended in the Belgian guidelines for economic evaluations, produces somewhat better results than equal discounting at 3% or 5% for costs and effects.



Table 74 – Results of the economic evaluation for different discount rates (time horizon 10 years)

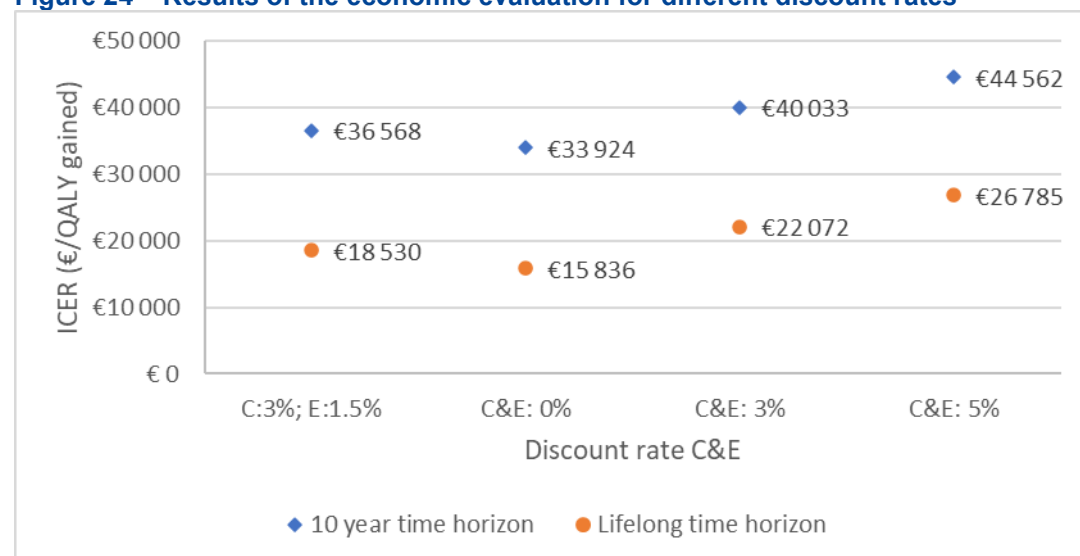
Discount rate	Cost comparator	Cost intervention	Incremental cost	LYs comparator	LYs intervention	IE (LYG)	ICER (€/LYG)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	QALYs comparator mean (2.5% - 97.5%)	QALYs intervention mean (2.5% - 97.5%)	IE (QALYs gained) mean (2.5% - 97.5%)	ICER (€/QALY gained) mean (2.5% - 97.5%)
C: 3%	€87.305	€163.345	€76.040	5,91	9,03	3,12	€25.006
E: 1.5%	(72.373 - 102.666)	(152.662 - 175.339)	(67.568 - 84.637)	(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(16.983 - 36.179)
				4,59	6,92	2,34	€36.568
				(2,16 - 6,29)	(3,24 - 9,56)	(1,00 - 3,49)	(19.767 - 76.603)
C&E: 0%	€95.270	€172.616	€77.345	6,31	9,71	3,39	€23.421
	(78.866 - 112.143)	(161.033 - 185.430)	(68.417 - 86.475)	(5,26 - 7,42)	(8,15 - 11,50)	(2,49 - 4,38)	(15.847 - 33.978)
				4,90	7,46	2,56	€33.924
				(2,31 - 6,71)	(3,49 - 10,30)	(1,11 - 3,81)	(18.394 - 70.711)
C&E: 3%	€87.305	€163.345	€76.040	5,54	8,43	2,88	€27.098
	(72.373 - 102.666)	(152.662 - 175.339)	(67.568 - 84.637)	(4,61 - 6,52)	(7,10 - 9,99)	(2,12 - 3,72)	(18.406 - 39.233)
				4,30	6,44	2,14	€40.033
				(2,03 - 5,89)	(3,01 - 8,92)	(0,90 - 3,20)	(21.514 - 84.816)
C&E: 5%	€82.688	€157.916	€75.228	5,11	7,71	2,60	€29.720
	(68.693 - 97.373)	(147.747 - 169.497)	(66.896 - 83.499)	(4,27 - 6,01)	(6,50 - 9,14)	(1,91 - 3,36)	(20.249 - 43.048)
				3,97	5,88	1,91	€44.562
				(1,87 - 5,44)	(2,74 - 8,15)	(0,79 - 2,87)	(23.738 - 94.869)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.


Table 75 – Results of the economic evaluation for different discount rates (lifelong time horizon)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Discount rate							
C: 3%	€100.808	€178.554	€77.747	8,94	14,89	5,95	€13.420
E: 1.5%	(83.614 - 118.595)	(166.000 - 192.785)	(69.033 - 86.348)	(7,42 - 10,56)	(12,26 - 17,66)	(4,39 - 7,65)	(9.235 - 19.036)
				6,96	11,60	4,64	€18.530
				(3,29 - 9,58)	(5,49 - 16,07)	(2,14 - 6,83)	(10.413 - 37.340)
C&E: 0%	€118.262	€198.778	€80.516	10,31	17,45	7,14	€11.579
	(98.390 - 138.703)	(183.640 - 215.867)	(70.831 - 89.785)	(8,53 - 12,17)	(14,30 - 20,71)	(5,28 - 9,17)	(7.986 - 16.552)
				8,02	13,63	5,61	€15.836
				(3,79 - 11,07)	(6,46 - 18,85)	(2,63 - 8,25)	(9.044 - 31.950)
C&E: 3%	€100.808	€178.554	€77.747	7,88	12,93	5,04	€15.820
	(83.614 - 118.595)	(166.000 - 192.785)	(69.033 - 86.348)	(6,55 - 9,30)	(10,69 - 15,33)	(3,73 - 6,48)	(10.899 - 22.537)
				6,13	10,03	3,90	€22.072
				(2,90 - 8,44)	(4,74 - 13,91)	(1,78 - 5,76)	(12.322 - 44.469)
C&E: 5%	€92.440	€168.840	€76.400	6,80	10,94	4,15	€18.912
	(76.847 - 108.442)	(157.392 - 181.995)	(67.883 - 84.754)	(5,65 - 8,01)	(9,10 - 12,97)	(3,06 - 5,32)	(13.070 - 26.990)
				5,28	8,46	3,17	€26.785
				(2,50 - 7,26)	(3,98 - 11,72)	(1,42 - 4,70)	(14.847 - 54.101)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

**Figure 24 – Results of the economic evaluation for different discount rates**

C: costs; E: effects; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

6.2.3. Invitation and communication costs

Table 76 and Table 77 show the impact of changing the invitation or communication costs. A somewhat increased cost for the invitation or communication (e.g. as reported by BruPrev and CCRef for Brussels and Wallonia respectively) does not have a major impact on ICERs. In contrast, excluding invitation costs, as found in the economic literature review, does

have a greater impact on cost-effectiveness (Figure 25). Excluding this cost leads to an (unjustified) improvement in cost-effectiveness from about €37 000 per QALY gained to about €27 000 per QALY gained (10-year time horizon). When applying a lifetime time horizon, this is an (unjustified) decrease from about €19 000 per QALY gained to €14 000 per QALY gained. These are unjustified improvements of the ICER as the cost of the invitation is effectively part of the incremental cost of providing lung cancer screening.


Table 76 – Results of the economic evaluation for different invitation and communication costs (time horizon 10 years)

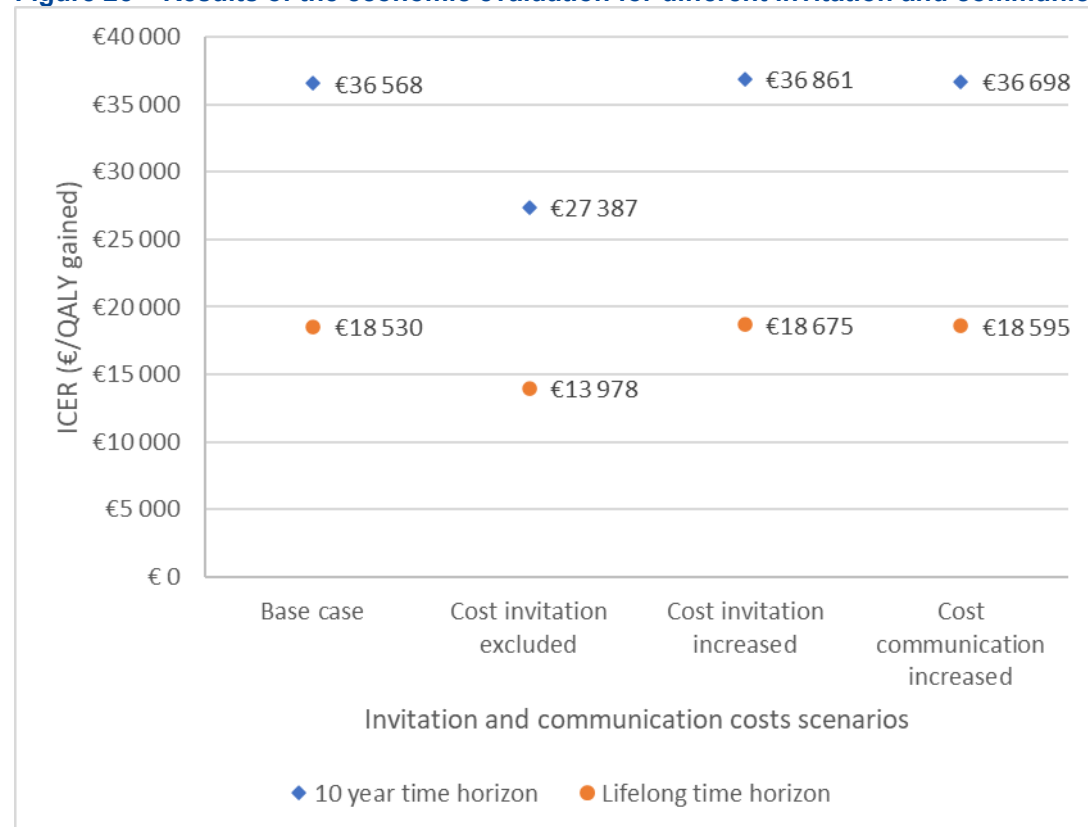
	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Cost invitation							
Base case	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€25.006 (16.983 - 36.179) €36.568 (19.767 - 76.603)
Excluded	€87.305 (72.373 - 102.666)	€144.162 (134.230 - 155.185)	€56.857 (48.430 - 64.337)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€18.739 (12.311 - 28.118) €27.387 (14.345 - 57.601)
Increased	€87.305 (72.373 - 102.666)	€163.957 (153.274 - 176.062)	€76.652 (68.075 - 85.299)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€25.206 (17.126 - 36.451) €36.861 (19.924 - 77.208)
Cost communication							
Base case	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€25.006 (16.983 - 36.179) €36.568 (19.767 - 76.603)
Increased	€87.305 (72.373 - 102.666)	€163.617 (152.903 - 175.561)	€76.312 (67.791 - 84.904)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€25.095 (17.063 - 36.321) €36.698 (19.846 - 76.918)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

**Table 77 – Results of the economic evaluation for different invitation and communication costs (lifelong time horizon)**

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Cost invitation							
Base case	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.420 (9.235 - 19.036) €18.530 (10.413 - 37.340)
Excluded	€100.808 (83.614 - 118.595)	€159.372 (147.152 - 172.699)	€58.564 (50.408 - 66.079)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€10.129 (6.728 - 14.990) €13.978 (7.679 - 28.398)
Increased	€100.808 (83.614 - 118.595)	€179.167 (166.558 - 193.479)	€78.359 (69.535 - 86.997)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.525 (9.315 - 19.173) €18.675 (10.498 - 37.634)
Cost communication							
Base case	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.420 (9.235 - 19.036) €18.530 (10.413 - 37.340)
Increased	€100.808 (83.614 - 118.595)	€178.826 (166.234 - 193.105)	€78.018 (69.319 - 86.600)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.467 (9.266 - 19.097) €18.595 (10.451 - 37.453)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

**Figure 25 – Results of the economic evaluation for different invitation and communication costs**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.



6.2.4. *Participation*

The base case analysis includes participation as in the NELSON trial. More than 600 000 people received an initial questionnaire about the trial. After an initial response from about 150 000 people, about 31 000 were eligible and invited to participate. About half of these invited persons (51.1%) eventually participated in the study. The cost in the intervention arm is expressed per 100 participants. With higher participation, the average cost of the invitation decreases, thus reducing the cost in the intervention arm (see Table 78 and Table 79). The effects are also expressed per 100 participants. Changing the participation probability thus does not influence the incremental effects. In the end, a lower participation of 30% results in an ICER of about €43 000 or €22 000 per QALY gained applying a 10-year or lifetime horizon, respectively (see Figure 26). If the participation would increase to about 70%, this would become about €34 000 or €17 000 per QALY gained, respectively.


Table 78 – Results of the economic evaluation for different participation probabilities (time horizon 10 years)

Participation	Cost comparator	Cost intervention**	Incremental cost	LYs comparator	LYs intervention	IE (LYG)	ICER (€/LYG)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
30%	€87.305 (72.373 - 102.666)	€176.844 (165.062 - 190.078)	€89.539 (79.711 - 99.717)	5,91	9,03	3,12	€29.416
				(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(20.306 - 42.102)
				4,59 (2,16 - 6,29)	6,92 (3,24 - 9,56)	2,34 (1,00 - 3,49)	€43.029 (23.635 - 89.480)
40%	€87.305 (72.373 - 102.666)	€168.675 (157.695 - 180.872)	€81.370 (72.427 - 90.429)	5,91	9,03	3,12	€26.747
				(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(18.433 - 38.389)
				4,59 (2,16 - 6,29)	6,92 (3,24 - 9,56)	2,34 (1,00 - 3,49)	€39.119 (21.365 - 81.359)
51.11%*	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91	9,03	3,12	€25.006
				(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(16.983 - 36.179)
				4,59 (2,16 - 6,29)	6,92 (3,24 - 9,56)	2,34 (1,00 - 3,49)	€36.568 (19.767 - 76.603)
60%	€87.305 (72.373 - 102.666)	€160.498 (150.048 - 172.376)	€73.193 (64.946 - 81.486)	5,91	9,03	3,12	€24.076
				(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(16.305 - 34.936)
				4,59 (2,16 - 6,29)	6,92 (3,24 - 9,56)	2,34 (1,00 - 3,49)	€35.206 (18.933 - 73.929)
70%	€87.305 (72.373 - 102.666)	€158.165 (147.878 - 169.602)	€70.860 (62.629 - 78.927)	5,91	9,03	3,12	€23.314
				(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(15.687 - 34.007)
				4,59 (2,16 - 6,29)	6,92 (3,24 - 9,56)	2,34 (1,00 - 3,49)	€34.089 (18.280 - 71.859)
80%	€87.305 (72.373 - 102.666)	€156.416 (146.275 - 167.671)	€69.111 (60.942 - 76.901)	5,91	9,03	3,12	€22.743
				(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(15.245 - 33.268)
				4,59 (2,16 - 6,29)	6,92 (3,24 - 9,56)	2,34 (1,00 - 3,49)	€33.251 (17.764 - 70.170)
90%	€87.305 (72.373 - 102.666)	€155.053 (144.959 - 166.165)	€67.748 (59.521 - 75.283)	5,91	9,03	3,12	€22.297
				(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(14.908 - 32.690)
				4,59 (2,16 - 6,29)	6,92 (3,24 - 9,56)	2,34 (1,00 - 3,49)	€32.599 (17.385 - 68.879)

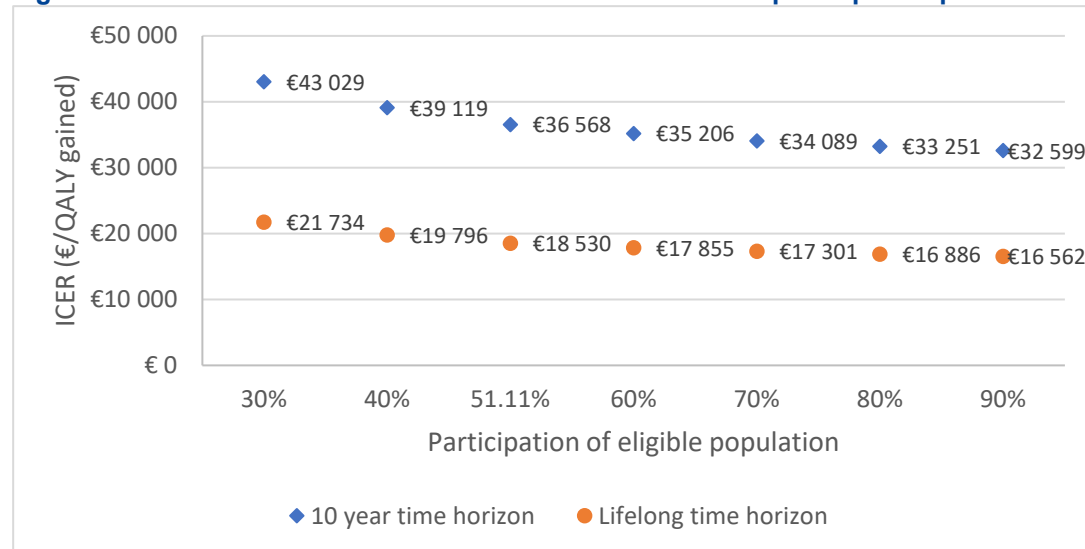
* Base case. ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

**Table 79 – Results of the economic evaluation for different participation probabilities (lifelong time horizon)**

Participation	Cost comparator	Cost intervention	Incremental cost	LYs comparator	LYs intervention	IE (LYG)	ICER (€/LYG)
				QALYs comparator	QALYs intervention	IE (QALYs gained)	ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
30%	€100.808 (83.614 - 118.595)	€192.053 (178.306 - 207.347)	€91.245 (80.845 - 101.549)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€15.735 (10.986 - 22.374) €21.734 (12.367 - 43.683)
40%	€100.808 (83.614 - 118.595)	€183.885 (170.739 - 198.544)	€83.077 (73.753 - 92.317)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€14.334 (9.928 - 20.370) €19.796 (11.188 - 39.795)
51.11%*	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.420 (9.235 - 19.036) €18.530 (10.413 - 37.340)
60%	€100.808 (83.614 - 118.595)	€175.708 (163.145 - 189.738)	€74.900 (66.471 - 83.326)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€12.932 (8.857 - 18.420) €17.855 (10.048 - 35.946)
70%	€100.808 (83.614 - 118.595)	€173.375 (160.791 - 187.112)	€72.567 (64.098 - 80.663)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€12.531 (8.571 - 17.957) €17.301 (9.719 - 34.865)
80%	€100.808 (83.614 - 118.595)	€171.626 (159.133 - 185.388)	€70.818 (62.276 - 78.765)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€12.231 (8.339 - 17.610) €16.886 (9.458 - 34.035)
90%	€100.808 (83.614 - 118.595)	€170.263 (157.867 - 183.939)	€69.455 (61.124 - 77.354)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€11.998 (8.169 - 17.324) €16.562 (9.255 - 33.464)

* Base case. ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

Figure 26 – Results of the economic evaluation for different participation probabilities



ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

6.2.5. Adherence

In the NELSON trial, screening uptake was 95.7%, 94% and 91.5% over the first three screening rounds, respectively. Reducing the screening uptake to 50% in the second and third round increases the ICER (see Table 80 and Table 81), because the incremental effects have proportionally reduced more than the incremental costs. The ICERs increase to about €42 000 or €22 000 per QALY gained, applying a 10-year or lifetime horizon, respectively (see Figure 27).

**Table 80 – Results of the economic evaluation for reduced adherence (time horizon 10 years)**

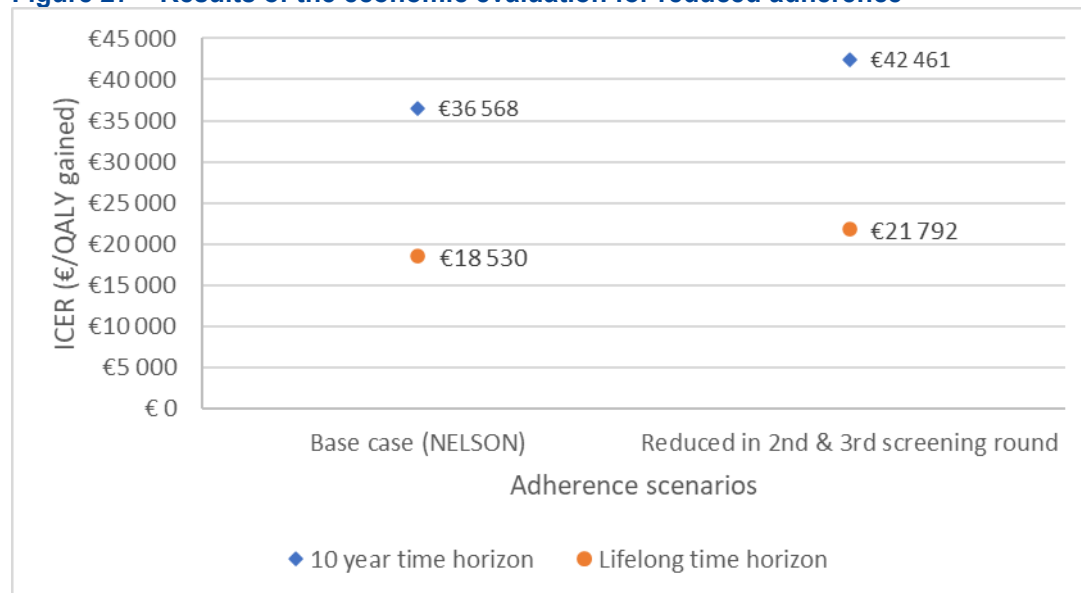
	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Adherence							
Base case	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€25.006 (16.983 - 36.179) €36.568 (19.767 - 76.603)
Reduced to 50% in the 2 nd & 3 rd round	€62.474 (51.584 - 74.181)	€123.408 (114.819 - 133.253)	€60.934 (54.074 - 67.640)	4,24 (3,51 - 5,03) 3,29 (1,58 - 4,53)	6,46 (5,37 - 7,72) 4,92 (2,26 - 6,92)	2,22 (1,61 - 2,87) 1,63 (0,67 - 2,50)	€28.283 (19.251 - 40.838) €42.461 (22.467 - 95.264)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

Table 81 – Results of the economic evaluation for reduced adherence (lifelong time horizon)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Adherence							
Base case	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.420 (9.235 - 19.036) €18.530 (10.413 - 37.340)
Reduced to 50% in the 2 nd & 3 rd round	€71.738 (59.509 - 84.976)	€133.873 (124.039 - 145.402)	€62.136 (54.992 - 68.903)	6,32 (5,22 - 7,46) 4,92 (2,37 - 6,77)	10,42 (8,61 - 12,49) 8,08 (3,81 - 11,31)	4,11 (2,99 - 5,29) 3,17 (1,41 - 4,74)	€15.552 (10.740 - 21.918) €21.792 (12.106 - 45.522)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

**Figure 27 – Results of the economic evaluation for reduced adherence**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

6.2.6. Overdiagnosis

Table 82 and Table 83 show the impact of different overdiagnosis. Applying a different overdiagnosis has an important impact on the ICERs since screen-detected cancers that are classified as an overdiagnosis leads only to costs but not to benefits in the economic model. If there is less overdiagnosis, more patients are included in the model for which the stage shift is modelled leading to a greater benefit in the intervention group (or vice versa). The costs in the intervention group are influenced by the combination of treatment costs and survival time that depends on lung cancer stages and histology. A smaller overdiagnosis group in the lung cancer screening arm means more cancers are modelled in the comparator group in the model.

This raises costs in the comparator arm of the model (see Table 82 and Table 83). In the end, if the overdiagnosis would be 8.87%, the ICERs would become about €23 000 or €12 000 per QALY gained, applying a 10-year or lifetime horizon, respectively. If the overdiagnosis would be 38%, this becomes about €55 000 or €28 000 per QALY gained, respectively (see Figure 28).

We note that the validation of these scenarios shows that all evidence on lung cancer staging and histology remains respected (see part 6.2.12).

**Table 82 – Results of the economic evaluation for overdiagnosis scenarios (time horizon 10 years)**

	Cost comparator	Cost intervention	Incremental cost	LYs comparator	LYs intervention	IE (LYG)	ICER (€/LYG)
				QALYs comparator	QALYs intervention	IE (QALYs gained)	ICER (€/QALY gained)
	mean	mean	mean	mean	mean	mean	mean
	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)
Overdiagnosis							
23,87%	€87.305	€163.345	€76.040	5,91	9,03	3,12	€25.006
	(72.373 - 102.666)	(152.662 - 175.339)	(67.568 - 84.637)	(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(16.983 - 36.179)
				4,59	6,92	2,34	€36.568
				(2,16 - 6,29)	(3,24 - 9,56)	(1,00 - 3,49)	(19.767 - 76.603)
8,87%	€105.464	€172.432	€66.968	7,06	11,25	4,19	€16.308
	(88.346 - 123.521)	(160.621 - 185.374)	(57.612 - 76.560)	(6,00 - 8,21)	(9,52 - 13,14)	(3,28 - 5,18)	(11.422 - 23.088)
				5,48	8,71	3,23	€22.839
				(2,65 - 7,50)	(4,13 - 11,94)	(1,47 - 4,56)	(12.996 - 46.497)
19,70%	€92.369	€165.881	€73.513	6,23	9,65	3,42	€22.030
	(77.486 - 109.137)	(154.789 - 178.005)	(64.197 - 82.165)	(5,27 - 7,31)	(8,07 - 11,44)	(2,59 - 4,37)	(14.857 - 30.739)
				4,84	7,42	2,59	€31.742
				(2,32 - 6,55)	(3,49 - 10,20)	(1,13 - 3,82)	(17.526 - 67.857)
38,00%	€70.970	€155.171	€84.202	4,88	7,04	2,16	€63.057
	(38.036 - 99.743)	(137.500 - 172.334)	(68.593 - 102.073)	(2,80 - 6,80)	(3,05 - 10,54)	(0,19 - 4,00)	(15.357 - 265.363)
				3,79	5,32	1,53	€55.021*
				(1,61 - 5,94)	(1,83 - 9,25)	(-0,14 - 3,27)	

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

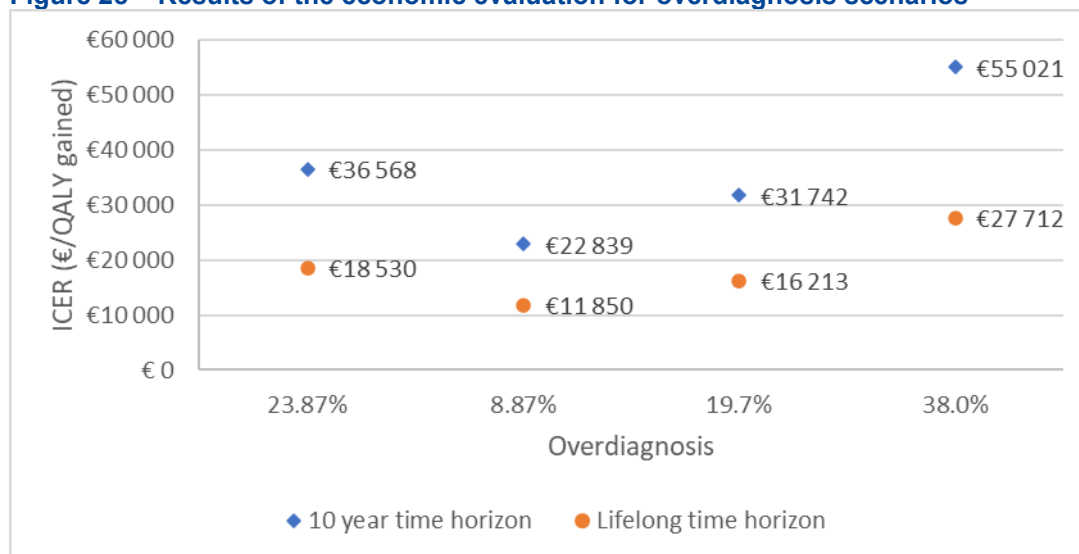
* The calculation of the average ICER based on the 1000 simulations is not reliable if the outcomes are situated in different quadrants. In these cases, the presented ICERs are calculated by dividing the mean incremental cost by the mean incremental benefit.


Table 83 – Results of the economic evaluation for overdiagnosis scenarios (lifelong time horizon)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Overdiagnosis							
23,87%	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.420 (9.235 - 19.036) €18.530 (10.413 - 37.340)
8,87%	€121.763 (102.554 - 142.290)	€190.721 (176.476 - 206.750)	€68.958 (59.582 - 78.332)	10,69 (8,97 - 12,46) 8,31 (4,01 - 11,39)	18,70 (15,84 - 21,79) 14,67 (7,06 - 20,02)	8,02 (6,28 - 9,86) 6,35 (3,02 - 8,90)	€8.772 (6.247 - 12.324) €11.850 (6.894 - 23.914)
19,70%	€106.653 (89.732 - 126.115)	€181.950 (168.611 - 197.180)	€75.297 (65.949 - 83.700)	9,43 (7,91 - 11,13) 7,34 (3,52 - 9,95)	15,95 (13,25 - 18,87) 12,46 (5,89 - 17,05)	6,53 (4,93 - 8,27) 5,12 (2,36 - 7,42)	€11.825 (8.056 - 16.454) €16.213 (9.183 - 33.561)
38,00%	€81.956 (43.915 - 115.185)	€167.606 (145.490 - 190.152)	€85.650 (70.166 - 103.132)	7,37 (4,21 - 10,29) 5,74 (2,42 - 8,98)	11,46 (4,62 - 17,50) 8,83 (2,84 - 15,47)	4,08 (0,30 - 7,65) 3,09 (-0,07 - 6,43)	€36.040 (8.283 - 143.109) €27.712*

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

* The calculation of the average ICER based on the 1000 simulations is not reliable if the outcomes are situated in different quadrants. In these cases, the presented ICERs are calculated by dividing the mean incremental cost by the mean incremental benefit.

**Figure 28 – Results of the economic evaluation for overdiagnosis scenarios**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.



6.2.7. Quality of life

Table 84 and Table 85 present the impact of changing the input for QoL variables. In the study of Blom et al.,²⁰⁸ the QoL difference between stage I and IV lung cancers was higher. However, on the other hand, this study made no difference between utilities for stage III or IV lung cancers and the utilities were lower than those presented by Tramontano et al.¹⁹⁶ resulting in lower QALYs. Applying the utilities as presented by Blom et al.²⁰⁸ results in somewhat lower ICERs of about €34 000 or €18 000 per QALY gained, applying a 10-year or lifetime horizon, respectively.

Greater disutility for false positive and indeterminate findings increases the ICERs (and vice versa). Ignoring this disutility, which we consider unjustified for the base case, leads to an average ICER of about €32 000 or €17 000 per QALY gained, applying a 10-year or lifetime horizon, respectively. Increasing this disutility results in an average ICER of about €45 000 or €20 000 per QALY gained, respectively (see Figure 29).

Remark: We had no information on the loss of quality of life associated with overdiagnosis compared to the situation where the cancer would not be diagnosed (e.g., as a result of being confronted with a cancer diagnosis and undergoing cancer treatment). The impact was also not modelled in a hypothetical way (see part 6.1.7.9). After conducting the economic evaluation, a 1000-person figure was constructed to transparently present the impact of lung cancer screening (see part 8). On this figure, we see that the number of participants affected by an undetermined or false positive result is much higher than the number of overdiagnoses. In the base case, this translates to 266 versus 6 participants, respectively, out of a total of 1000 people. Should evidence become available on the impact of overdiagnosis and overtreatment, the magnitude of the impact on the ICERs can be estimated from the presented scenarios where the QoL for false positives and indeterminate findings was modified. For example, if overdiagnosis were associated with an additional quality-of-life loss of 0.05 or 0.10 (arbitrary values for this hypothetical example) for 12 months for these 6 people, the impact will be smaller than the impact of a quality-of-life loss of about 0.03 for 3 months for 266 people. This way, researchers can have an idea of the potential impact if they have better QoL data linked to overdiagnosis without having to rebuild the economic model.



Table 84 – Results of the economic evaluation for QoL scenarios (time horizon 10 years)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator	LYs intervention	IE (LYG)	ICER (€/LYG)
				QALYs comparator	QALYs intervention	IE (QALYs gained)	ICER (€/QALY gained)
	mean	mean	mean	mean	mean	mean	mean
	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)	(2.5% - 97.5%)
QoL st.I-IV							
Tramontano et al.	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€25.006 (16.983 - 36.179) €36.568 (19.767 - 76.603)
Blom et al.	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,32 (3,53 - 5,16)	9,03 (7,60 - 10,71) 6,63 (5,32 - 8,06)	3,12 (2,29 - 4,03) 2,31 (1,54 - 3,14)	€25.006 (16.983 - 36.179) €34.278 (22.132 - 53.264)
QoL false positive and indeterminate findings							
0.0307	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€25.006 (16.983 - 36.179) €36.568 (19.767 - 76.603)
0.0000	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 7,18 (3,48 - 9,85)	3,12 (2,29 - 4,03) 2,59 (1,29 - 3,75)	€25.006 (16.983 - 36.179) €31.930 (18.509 - 61.402)
0.0630	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,66 (2,95 - 9,33)	3,12 (2,29 - 4,03) 2,07 (0,76 - 3,23)	€25.006 (16.983 - 36.179) €44.517 (21.509 - 104.006)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year; QoL: quality of life; st.: stage.

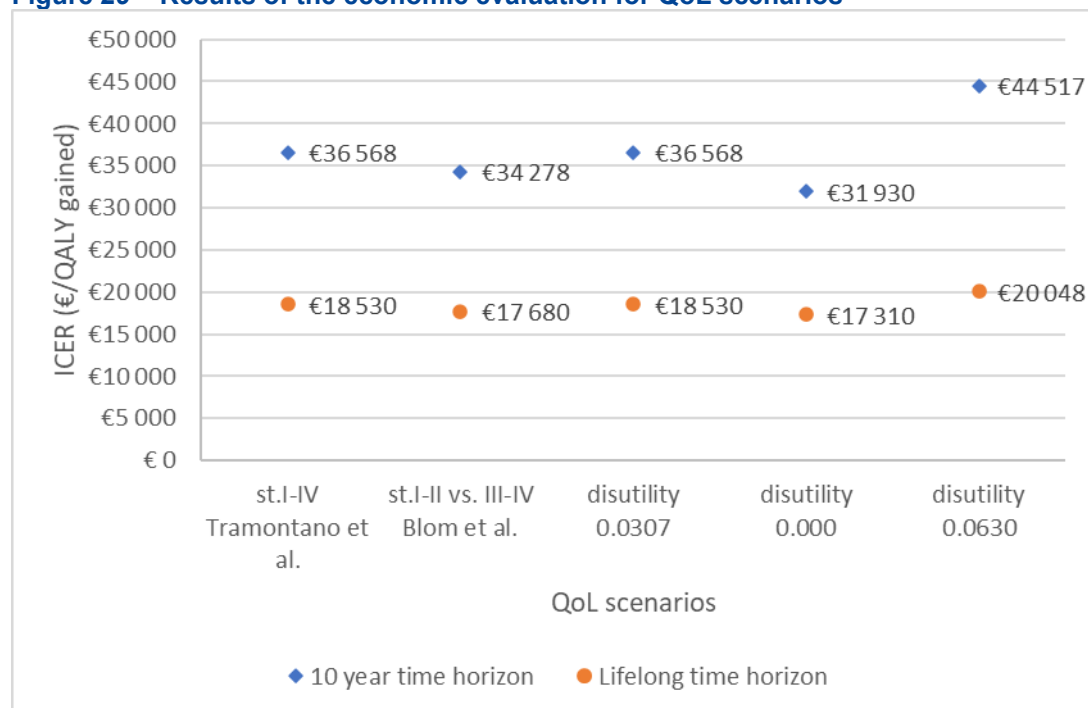

Table 85 – Results of the economic evaluation for QoL scenarios (lifelong time horizon)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
QoL st.I-IV							
Tramontano et al.	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.420 (9.235 - 19.036) €18.530 (10.413 - 37.340)
Blom et al.	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,57 (5,33 - 7,89)	14,89 (12,26 - 17,66) 11,12 (8,85 - 13,51)	5,95 (4,39 - 7,65) 4,55 (3,14 - 6,00)	€13.420 (9.235 - 19.036) €17.680 (11.737 - 26.620)
QoL false positive and indeterminate findings							
0.0307	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.420 (9.235 - 19.036) €18.530 (10.413 - 37.340)
0.0000	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,85 (5,73 - 16,23)	5,95 (4,39 - 7,65) 4,89 (2,39 - 7,11)	€13.420 (9.235 - 19.036) €17.310 (10.076 - 33.461)
0.0630	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,33 (5,21 - 15,71)	5,95 (4,39 - 7,65) 4,37 (1,87 - 6,58)	€13.420 (9.235 - 19.036) €20.048 (10.868 - 42.828)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year; QoL: quality of life; st.: stage.



Figure 29 – Results of the economic evaluation for QoL scenarios



ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; QoL: quality of life; st.: stage; vs.: versus.

6.2.8. Price discount

Table 86 and Table 87 present the impact of changing the price discount for the systemic therapy costs. Applying a larger price discount for costs in the systemic therapy category has, in comparison with the other performed scenario analyses, a stronger impact on the cost-effectiveness of lung cancer screening. The costs for this category are relatively large compared to all other cost categories. The larger the discount, the smaller the cost savings generated through the stage shift. This results in a higher incremental cost and thus higher ICERs (see Figure 30).


Table 86 – Results of the economic evaluation for price discount scenarios (time horizon 10 years)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
Discount syst. therapy	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
no discount	€130.828 (108.057 - 154.182)	€187.393 (172.804 - 203.667)	€56.564 (42.660 - 70.172)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€18.775 (10.603 - 30.053) €27.481 (12.836 - 60.358)
10%	€119.947 (99.107 - 141.190)	€181.381 (167.651 - 196.534)	€61.433 (48.954 - 73.783)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€20.333 (12.208 - 31.583) €29.753 (14.606 - 64.020)
20%	€109.066 (90.160 - 128.257)	€175.369 (162.679 - 189.326)	€66.302 (55.056 - 77.510)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€21.891 (13.809 - 33.113) €32.024 (16.372 - 67.750)
30%	€98.186 (81.394 - 115.374)	€169.357 (157.628 - 182.289)	€71.171 (61.422 - 80.932)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€23.448 (15.420 - 34.646) €34.296 (18.084 - 72.354)
40%	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€25.006 (16.983 - 36.179) €36.568 (19.767 - 76.603)



	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
Discount syst. therapy	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
50%	€76.424 (63.502 - 89.871)	€157.333 (147.744 - 168.402)	€80.909 (73.708 - 88.233)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€26.564 (18.562 - 37.708) €38.839 (21.447 - 80.860)
60%	€65.543 (54.609 - 76.935)	€151.321 (142.792 - 161.148)	€85.778 (79.473 - 92.158)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€28.122 (20.149 - 39.236) €41.111 (23.188 - 85.118)
70%	€54.663 (45.689 - 64.058)	€145.309 (137.392 - 154.103)	€90.646 (85.358 - 96.213)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€29.680 (21.784 - 40.764) €43.382 (24.863 - 89.376)
80%	€43.782 (36.699 - 51.429)	€139.297 (131.934 - 146.876)	€95.515 (90.973 - 100.289)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€31.237 (23.339 - 42.220) €45.654 (26.544 - 94.797)
90%	€32.901 (27.822 - 38.421)	€133.285 (126.378 - 140.190)	€100.384 (96.164 - 104.722)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€32.795 (24.939 - 43.737) €47.926 (28.353 - 99.334)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year; syst. therapy: systemic therapy.


Table 87 – Results of the economic evaluation for price discount scenarios (lifelong time horizon)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
Discount syst. therapy	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
no discount	€151.843 (125.431 - 178.204)	€210.264 (192.436 - 229.895)	€58.421 (43.950 - 72.250)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€10.174 (5.908 - 15.928) €14.051 (6.935 - 30.187)
10%	€139.084 (114.992 - 163.297)	€202.337 (185.795 - 220.196)	€63.253 (50.376 - 75.729)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€10.986 (6.766 - 16.719) €15.171 (7.805 - 32.009)
20%	€126.325 (104.570 - 148.395)	€194.409 (179.224 - 211.100)	€68.084 (56.495 - 79.052)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€11.797 (7.593 - 17.452) €16.290 (8.673 - 33.793)
30%	€113.567 (94.088 - 133.485)	€186.482 (172.501 - 202.037)	€72.915 (62.950 - 82.784)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€12.609 (8.432 - 18.242) €17.410 (9.570 - 35.603)
40%	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.420 (9.235 - 19.036) €18.530 (10.413 - 37.340)

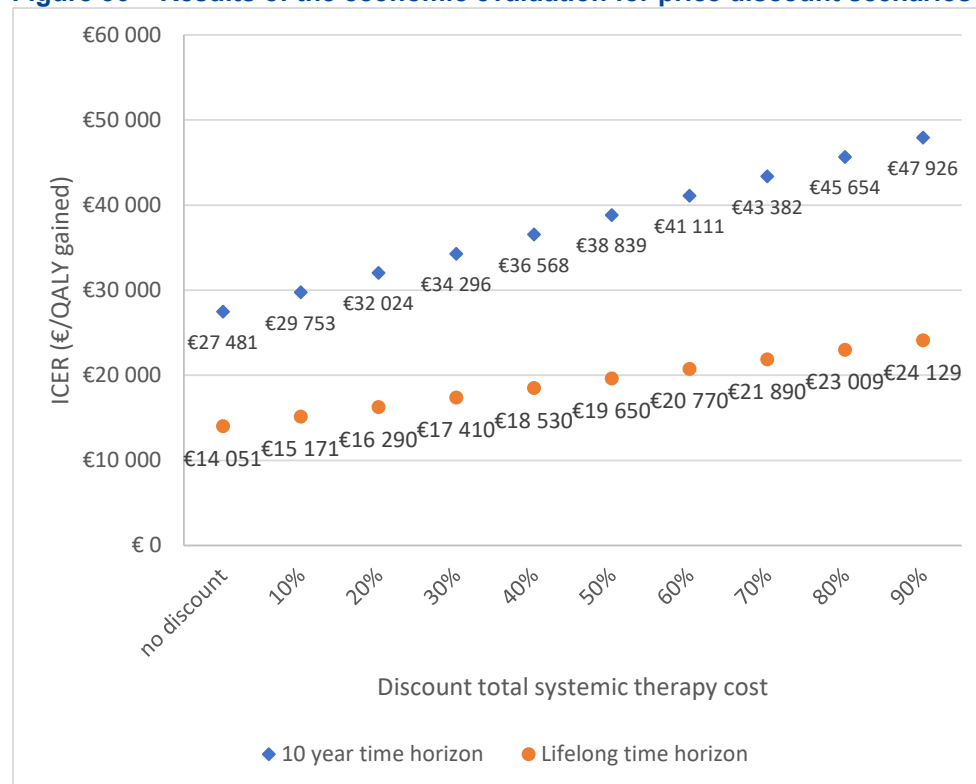


	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
Discount syst. therapy	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
50%	€88.049 (73.133 - 103.518)	€170.627 (159.354 - 183.985)	€82.578 (74.981 - 89.878)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€14.231 (10.086 - 19.831) €19.650 (11.282 - 38.948)
60%	€75.290 (62.608 - 88.420)	€162.699 (152.569 - 174.520)	€87.409 (80.932 - 93.743)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€15.043 (10.911 - 20.633) €20.770 (12.148 - 40.996)
70%	€62.532 (52.190 - 73.291)	€154.772 (145.872 - 165.138)	€92.240 (86.735 - 97.711)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€15.854 (11.702 - 21.446) €21.890 (13.045 - 42.850)
80%	€49.773 (41.791 - 58.144)	€146.845 (138.790 - 155.805)	€97.072 (92.532 - 101.674)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€16.666 (12.563 - 22.281) €23.009 (13.928 - 44.847)
90%	€37.014 (31.194 - 43.134)	€138.917 (131.438 - 146.798)	€101.903 (97.579 - 106.246)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€17.477 (13.402 - 23.069) €24.129 (14.826 - 47.133)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year; syst. therapy: systemic therapy.



Figure 30 – Results of the economic evaluation for price discount scenarios



ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

6.2.9. Supplements

Table 88 and Table 89 present the impact of ex-/including supplements paid by the patient. The impact is similar to the price discount. The higher the cost of advanced stage treatment, the greater the savings from a stage shift, resulting in better ICERs. Hence, including supplements leads to lower ICERs (Figure 31).

**Table 88 – Results of the economic evaluation for ex-/inclusion of supplements (time horizon 10 years)**

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Supplements							
Base case (excluded)	€87.305 (72.373 - 102.666)	€163.345 (152.662 - 175.339)	€76.040 (67.568 - 84.637)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€25.006 (16.983 - 36.179) €36.568 (19.767 - 76.603)
Inclusion of supplements	€131.802 (109.928 - 155.087)	€190.185 (175.516 - 206.134)	€58.384 (45.164 - 71.686)	5,91 (4,92 - 6,95) 4,59 (2,16 - 6,29)	9,03 (7,60 - 10,71) 6,92 (3,24 - 9,56)	3,12 (2,29 - 4,03) 2,34 (1,00 - 3,49)	€19.359 (11.484 - 30.938) €28.355 (13.221 - 62.133)

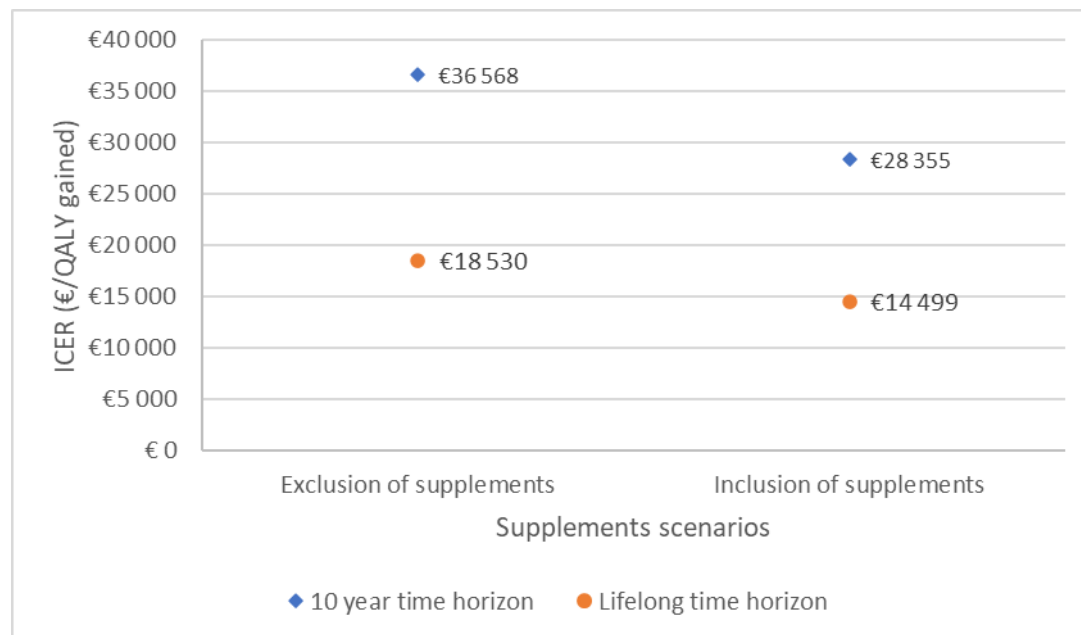
ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

Table 89 – Results of the economic evaluation for ex-/inclusion of supplements (lifelong time horizon)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Supplements							
Base case (excluded)	€100.808 (83.614 - 118.595)	€178.554 (166.000 - 192.785)	€77.747 (69.033 - 86.348)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€13.420 (9.235 - 19.036) €18.530 (10.413 - 37.340)
Inclusion of supplements	€152.910 (127.029 - 179.857)	€213.203 (194.785 - 233.174)	€60.293 (46.835 - 73.796)	8,94 (7,42 - 10,56) 6,96 (3,29 - 9,58)	14,89 (12,26 - 17,66) 11,60 (5,49 - 16,07)	5,95 (4,39 - 7,65) 4,64 (2,14 - 6,83)	€10.488 (6.330 - 16.405) €14.499 (7.153 - 31.056)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

Figure 31 – Results of the economic evaluation for ex-/inclusion of supplements



ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

6.2.10. Lead time

Table 90 and Table 91 present the results of the exploratory analysis related to the lead time. As mentioned in part 6.1.7.11, only an impact on the costs in the comparator group is modelled through an increase of the lead time. This results in lower costs in the comparator group and thus higher incremental costs for lung cancer screening. Applying a 4-year lead time, the ICERs are about €41 000 or €21 000 per QALY gained applying a 10-year or lifetime horizon, respectively (see Figure 32).

**Table 90 – Results of the economic evaluation for lead time scenarios (time horizon 10 years)**

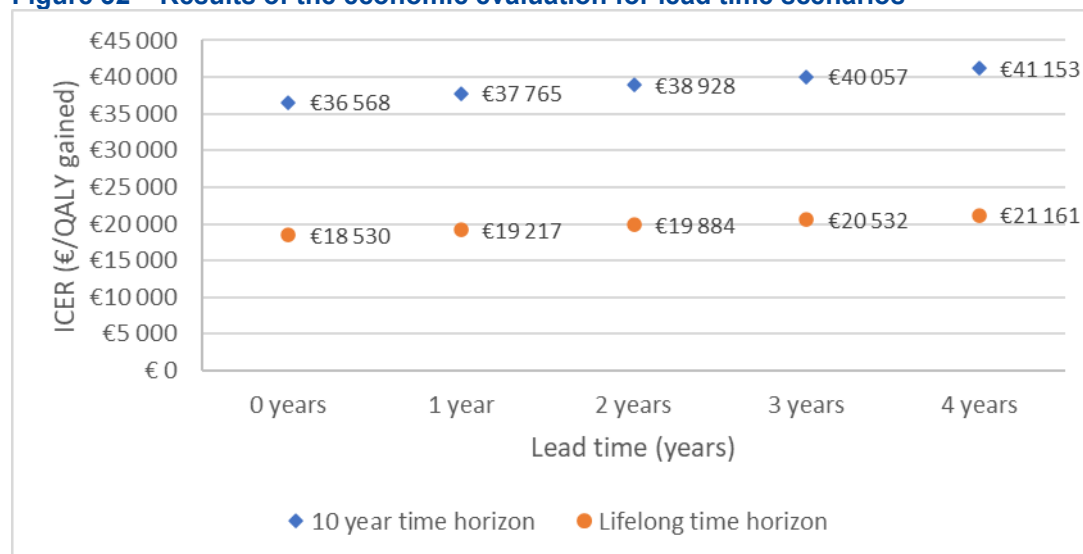
	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Lead time							
not taken	€87.305	€163.345	€76.040	5,91	9,03	3,12	€25.006
into account	(72.373 - 102.666)	(152.662 - 175.339)	(67.568 - 84.637)	(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(16.983 - 36.179)
				4,59	6,92	2,34	€36.568
				(2,16 - 6,29)	(3,24 - 9,56)	(1,00 - 3,49)	(19.767 - 76.603)
1 year	€84.762	€163.345	€78.583	5,91	9,03	3,12	€25.829
	(70.265 - 99.676)	(152.662 - 175.339)	(70.313 - 86.830)	(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(17.723 - 37.174)
				4,59	6,92	2,34	€37.765
				(2,16 - 6,29)	(3,24 - 9,56)	(1,00 - 3,49)	(20.558 - 78.786)
2 years	€82.293	€163.345	€81.052	5,91	9,03	3,12	€26.627
	(68.219 - 96.772)	(152.662 - 175.339)	(73.086 - 89.105)	(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(18.450 - 38.162)
				4,59	6,92	2,34	€38.928
				(2,16 - 6,29)	(3,24 - 9,56)	(1,00 - 3,49)	(21.350 - 80.906)
3 years	€79.896	€163.345	€83.448	5,91	9,03	3,12	€27.402
	(66.232 - 93.954)	(152.662 - 175.339)	(75.777 - 91.127)	(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(19.128 - 39.121)
				4,59	6,92	2,34	€40.057
				(2,16 - 6,29)	(3,24 - 9,56)	(1,00 - 3,49)	(22.109 - 82.965)
4 years	€77.569	€163.345	€85.775	5,91	9,03	3,12	€28.155
	(64.303 - 91.217)	(152.662 - 175.339)	(78.241 - 93.342)	(4,92 - 6,95)	(7,60 - 10,71)	(2,29 - 4,03)	(19.801 - 39.992)
				4,59	6,92	2,34	€41.153
				(2,16 - 6,29)	(3,24 - 9,56)	(1,00 - 3,49)	(22.872 - 84.963)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.


Table 91 – Results of the economic evaluation for lead time scenarios (lifelong time horizon)

	Cost comparator	Cost intervention	Incremental cost	LYs comparator QALYs comparator	LYs intervention QALYs intervention	IE (LYG) IE (QALYs gained)	ICER (€/LYG) ICER (€/QALY gained)
	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)	mean (2.5% - 97.5%)
Lead time							
not taken	€100.808	€178.554	€77.747	8,94	14,89	5,95	€13.420
into account	(83.614 - 118.595)	(166.000 - 192.785)	(69.033 - 86.348)	(7,42 - 10,56)	(12,26 - 17,66)	(4,39 - 7,65)	(9.235 - 19.036)
				6,96 (3,29 - 9,58)	11,60 (5,49 - 16,07)	4,64 (2,14 - 6,83)	€18.530 (10.413 - 37.340)
1 year	€97.872 (81.179 - 115.141)	€178.554 (166.000 - 192.785)	€80.683 (72.150 - 88.969)	8,94 (7,42 - 10,56)	14,89 (12,26 - 17,66)	5,95 (4,39 - 7,65)	€13.919 (9.676 - 19.635)
				6,96 (3,29 - 9,58)	11,60 (5,49 - 16,07)	4,64 (2,14 - 6,83)	€19.217 (10.901 - 38.393)
2 years	€95.021 (78.814 - 111.787)	€178.554 (166.000 - 192.785)	€83.533 (75.255 - 91.354)	8,94 (7,42 - 10,56)	14,89 (12,26 - 17,66)	5,95 (4,39 - 7,65)	€14.403 (10.105 - 20.216)
				6,96 (3,29 - 9,58)	11,60 (5,49 - 16,07)	4,64 (2,14 - 6,83)	€19.884 (11.375 - 39.416)
3 years	€92.254 (76.519 - 108.531)	€178.554 (166.000 - 192.785)	€86.301 (78.327 - 93.814)	8,94 (7,42 - 10,56)	14,89 (12,26 - 17,66)	5,95 (4,39 - 7,65)	€14.873 (10.530 - 20.761)
				6,96 (3,29 - 9,58)	11,60 (5,49 - 16,07)	4,64 (2,14 - 6,83)	€20.532 (11.835 - 40.616)
4 years	€89.567 (74.290 - 105.370)	€178.554 (166.000 - 192.785)	€88.988 (81.289 - 96.327)	8,94 (7,42 - 10,56)	14,89 (12,26 - 17,66)	5,95 (4,39 - 7,65)	€15.330 (10.946 - 21.282)
				6,96 (3,29 - 9,58)	11,60 (5,49 - 16,07)	4,64 (2,14 - 6,83)	€21.161 (12.257 - 41.783)

ICER: incremental cost-effectiveness ratio; IE: incremental effects; LY: life year; LYG: life year gained; QALY: quality-adjusted life year.

**Figure 32 – Results of the economic evaluation for lead time scenarios**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

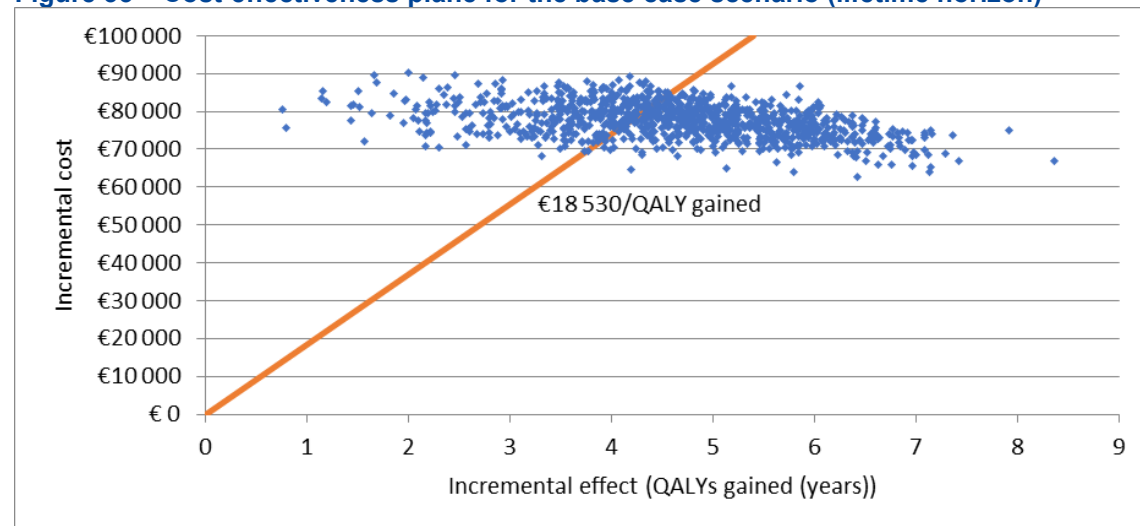
6.2.11. Cost-effectiveness plane and tornado graphs

Figure 33 shows the cost-effectiveness plane for the base case applying a lifetime time horizon, a participation rate as in NELSON (51%), an overdiagnosis rate of 23.9%, and a price discount for systemic therapy of 40%. There is an average incremental cost of about €78 000 and an incremental gain of about 4.6 QALYs per 100 participants. This results in an average ICER of €18 530 per QALY gained for lung cancer screening of high-risk (ex-)smokers in comparison to no screening.

Figure 34 presents the results on the cost-effectiveness acceptability curve. At a willingness to pay of €10 000 per QALY gained, there is a 1.5% probability that lung cancer screening is considered cost-effective. At a willingness to pay of €20 000 or €30 000 per QALY gained, this probability increases to 72% or 94%, respectively.

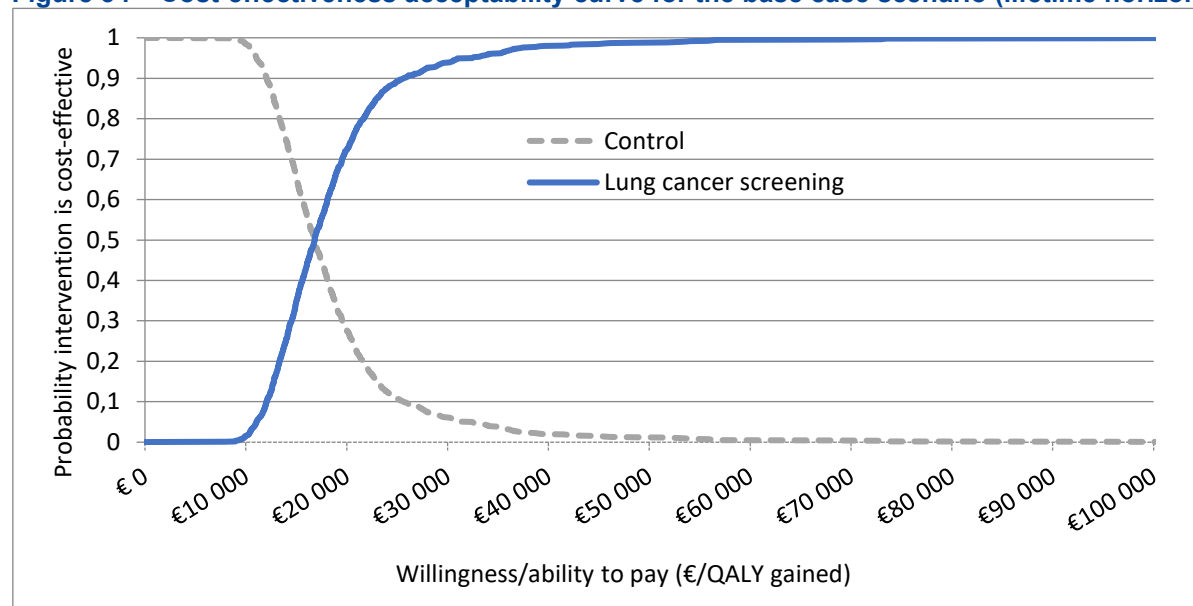


Figure 33 – Cost-effectiveness plane for the base case scenario (lifetime horizon)



QALY: *quality-adjusted life year*.

Figure 34 – Cost-effectiveness acceptability curve for the base case scenario (lifetime horizon)



QALY: quality-adjusted life year.

Figure 35 and Figure 36 present the tornado graphs summarizing the results of the performed scenario analyses for both a 10-year and lifetime horizon, respectively.

The percentage of overdiagnoses is the most influential variable. Applying a lifetime time horizon, increasing the overdiagnosis rate from 23.87% to 38% would increase the ICER from €18 530 per QALY gained to almost €28 000 per QALY gained (see Figure 36). Vice versa, a lower overdiagnosis rate of 8.87% would lower the ICER to about €12 000 per QALY gained.

Next, the price discount for systemic therapy has a relatively strong impact on the ICERs. The higher the price discount, the less cost-effective lung cancer screening becomes, and vice versa. Without applying the price discounts, the savings from screening by avoiding the more expensive

treatments, are overestimated. In line with this, inclusion of supplements paid by the patient improves the intervention's cost-effectiveness.

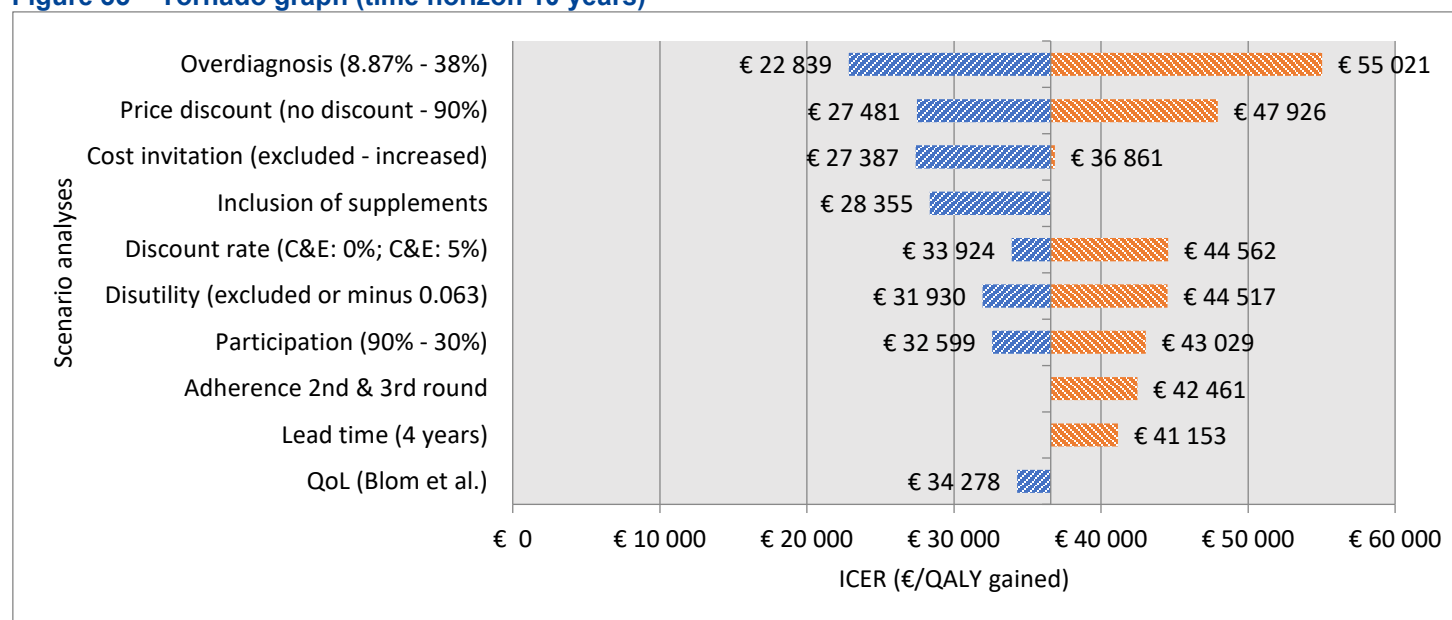
Furthermore, the tornado diagram shows the importance of taking into account the cost of reaching and inviting the target population. Not including this cost, which was the case in several of the economic evaluations identified in the literature review, results in too optimistic ICERs.

There are also variables with a relatively smaller impact, such as the participation rate and adherence throughout the screening programme. However, these variables were varied separately. Combining these two scenarios will obviously have a more important impact on the cost-effectiveness of lung cancer screening.



Finally, the exclusion or increase of the short-term disutility linked to false positive and indeterminate findings has a higher impact applying a 10-year time horizon in comparison with the lifetime time horizon. Vice versa, applying different discount rates for costs and effects has a higher impact applying the lifetime time horizon.

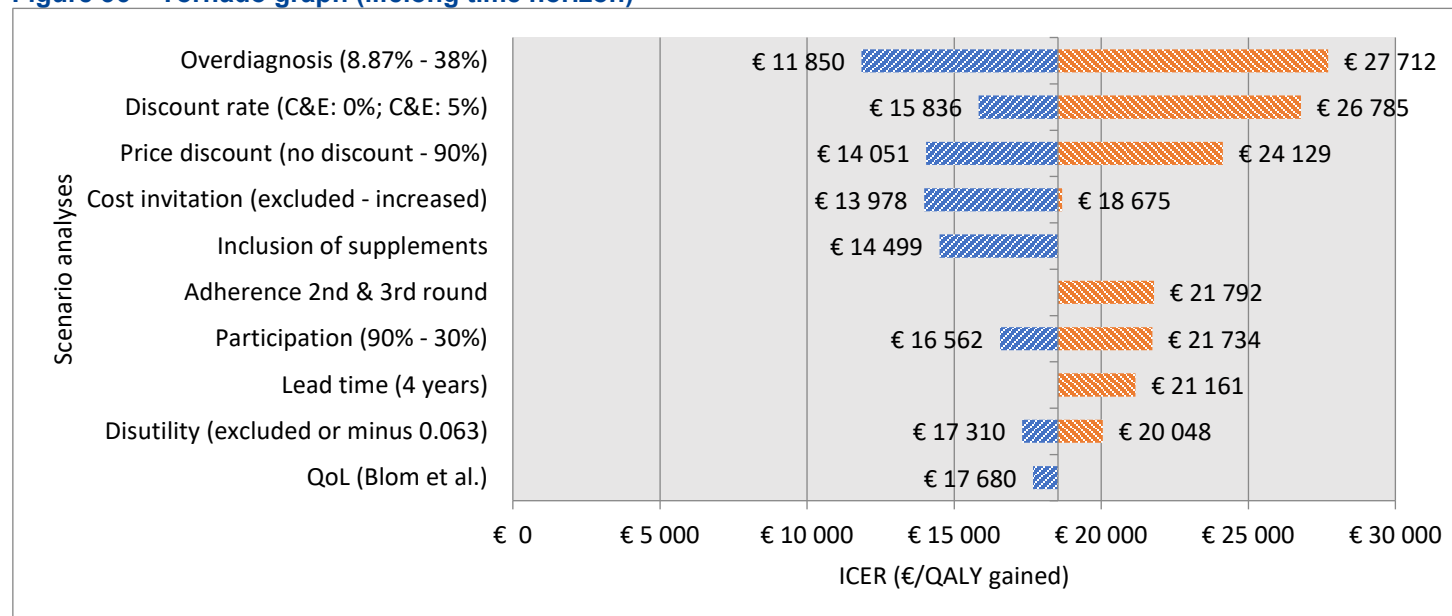
Figure 35 – Tornado graph (time horizon 10 years)



C: costs; E: effects; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; QoL: quality of life.
 Remark: applying a 10-year time horizon, the base case ICER is on average €36 568 per QALY gained.



Figure 36 – Tornado graph (lifelong time horizon)



C: costs; E: effects; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; QoL: quality of life.

Remark: applying a lifetime time horizon, the base case ICER is on average €18 530 per QALY gained.

6.2.12. Validation results

As indicated in the methodology, we also checked the specific intermediate outputs to verify the validity of our model. For the lung cancer screening group, these were the modelled total number of cancers, the number of screen-detected cancers and the number of interval cancers; the percentage (and number) of overdiagnoses; the stage and histology distribution of screen-detected cancers in the 3 screening rounds. For the control group these were the total number of cancers and the stage distribution of these cancers. In the following table we present the input for these variables as

well as the mean after 1000 simulations. These are thus not simply the input variables, which logically reflect the correct values, but rather the outcomes of the modelled cancers in the intervention and control group after applying all formulas (true positive findings, overdiagnosis, interval cancers, stages of screen-detected cancers and interval cancers, and correction for potential negative cells). The results in Table 92 show that the evidence was modelled correctly.


Table 92 – Overview of evidence-based values for input variables versus modelled values after 1000 simulations

Variable	Value	Source	Modelled average after 1000 simulations
Lung cancer screening group			Based on 7915 participants
• Total number of cancers (3 rounds)	N = 235	True positive findings + interval cancers	N = 235.62
• True positive findings (3 rounds)	N = 200 (1 st round: 70; 2 nd round: 55; 3 rd round: 75)	See part 6.1.7.3 (Table 47)	N = 200.59
• Interval cancers	N = 35 (1 st round: 5; 2 nd round: 7+12; 3 rd round: 7+4)	See part 6.1.7.3 (Table 47)	N = 35.03
• 1 st screening round:		See part 6.1.7.4 (Table 50)	
○ Stage I	64.9%		64.79%
○ Stage II	9.5%		9.57%
○ Stage III	18.9%		18.94%
○ Stage IV	6.8%		6.70%
○ NSCLC/SCLC	98.2%/1.8%		98.19%/1.81%
• 2 nd screening round:		See part 6.1.7.4 (Table 50)	
○ Stage I	75.9%		76.08%
○ Stage II	6.9%		6.78%
○ Stage III	13.8%		13.75%
○ Stage IV	3.4%		3.39%
○ NSCLC/SCLC	95.3%/4.7%		95.18%/4.82%
• 3 rd screening round:		See part 6.1.7.4 (Table 50)	
○ Stage I	72.7%		72.39%
○ Stage II	3.9%		3.99%
○ Stage III	19.5%		19.71%
○ Stage IV	3.9%		3.91%
○ NSCLC/SCLC	92.2%/7.8%		92.08%/7.92%
• Overdiagnosis	23.87%	See part 6.1.7.5 (Table 57)	23.97% (n=48.06)



Variable	Value	Source	Modelled average after 1000 simulations
Comparator group			
• Total number of cancers	/*	See part 6.1.7.4 (Table 50)	$N = 235.62 - 48.06 = 187.56$
○ Stage I	15.4%		15.43%
○ Stage II	10.7%		10.77%
○ Stage III	27.2%		27.20%
○ Stage IV	46.7%		46.60%
○ NSCLC/SCLC	/*		90.01%*/9.99%

* These variables are not modelled as an input, but are outcomes of the model after applying all formulas, i.e., after extraction of the overdiagnosis. The percentage of NSCLC is lower than in the intervention group since it was assumed that overdiagnosis comes entirely from the largest group of cancers, i.e., stage I, NSCLC (see part 6.1.7.7).

Second, the model was checked for negative cells. Modelling cancers by stage and histology might result in small cells. By subtracting the overdiagnosis, it was possible that a negative cell was created. Checking the 1000 simulations showed that this was the case in 8 simulations (<1%). Removing these simulations did not affect the results: the ICER from the base case scenario was €18 531 (compared to €18 530) per QALY gained. The percentage of overdiagnoses determined the number of simulations with negative cells. If an overdiagnosis rate of 38% was assumed, the number increased to 29/1000 simulations (~3%). When removing these simulations, the ICER became €27 152 (compared to €27 712) per QALY gained. Thus, the impact on the results is negligible.

Finally, we compared the gain in life years obtained from the stage-shift in the model with this gain being calculated in an alternative way (via the hazard ratio, see part 6.1.9). The difference was examined on the undiscounted results applying a 10-year time horizon. In the base case, with an overdiagnosis rate of 23.87%, lung cancer screening led to 3.39 undiscounted life years gained (see Table 74). When applying the alternative approach, this resulted in 3.95 life years gained (+0.56 LYG). In the scenario analysis assuming an overdiagnosis rate of 8.87%, the situation was reversed and the alternative method resulted in -0.60 LYG. The result of the alternative method is thus in between these two overdiagnosis scenarios. Consequently, we can conclude that the model does not generate illogical results.

Key points

In general:

- In the economic model, we applied the LDCT screening performance and the stage shift reported by the NELSON trial.

Cost information

- Cost data related to the identification and invitation of potential screen-eligible candidates were included in the economic evaluation. This cost data were provided by the Flanders Department of Care based on their experience with existing screening programmes and checked by experts from the other regions.
- Cost information related to LDCT scans is based on the 2024 nomenclature.
- Cost information was supplemented with data from the NELSON trial (e.g. procedures performed for false positive and indeterminate results)
- Costs related to the diagnosis and treatment of lung cancer (radiotherapy, surgery, systemic therapy and palliative care), per cancer stage and histology, were based on real-world Belgian data from lung cancer patients aged 50-75 years (BCR - IMA – AIM data).



Overall survival

- Overall survival, per cancer stage and histology, is based on data from Belgian lung cancer patients aged 50-75 years (BCR data).

Quality of life

- Both positive (i.e. through the stage shift) and negative (i.e. linked to false positive or indeterminate findings) consequences on QoL were included in the economic evaluation.
- QoL information is based on (short-term) information from the NELSON trial, information identified through the economic literature search, and supplemented with information from a targeted literature search.

Results

- In the base case analysis, applying a lifetime time horizon, lung cancer screening would result in an incremental cost of €77 747/100 participants and 4.64 QALYs gained/100 participants, resulting into an ICER of €18 530/QALY gained compared to no lung cancer screening.
- The cost-effectiveness acceptability curve indicates that lung cancer screening has a 1.5%, 72% and 94% probability of being cost-effective at a willingness to pay threshold of €10 000, €20 000 or €30 000 per QALY gained, respectively.
- The most determining variables are the overdiagnosis rate, the ex/inclusion of invitation costs, the price discounts for systemic therapy, and the participation rate and adherence throughout the screening programme.

Validation

- The validation exercise showed the model reflects the evidence extracted from the NELSON trial. Furthermore, the life years gained calculated via the stage shift are in line with the impact on all-cause mortality from the Cochrane meta-analysis.

7. ETHICAL CONSIDERATIONS

7.1. Method

Ethical considerations form part of the relevance criteria for setting up a screening programme developed by Jungner et al. and reviewed by Dobrow et al.^{9, 23, 24} This chapter aims to answer research question 3: 'What ethical issues must be considered in lung cancer screening'?

To provide an answer, a pragmatic search of the literature was carried out:

- Grey literature was analysed. We searched twenty websites of HTA institutes, which are members of the International Network of Agencies for Health Technology Assessment (INAHTA) in order to identify the existence of reports on the ethical evaluation of lung cancer screening or any methodological report on the evaluation of ethical aspects of health technologies or screening programmes.
- A search of the scientific literature was carried out in PUBMED/MEDLINE combining the text words "ethics" AND "screening" over the period 2013-2023.
- A book on the ethical aspects of screening²⁵⁰ was consulted.
- Two doctoral theses^{251, 252} on lung cancer screening were retrieved online from a university library (Erasmus University Rotterdam).

Moreover, one additional reference was selected via the bibliographies from the PUBMED/MEDLINE selection and two were provided^{253, 254} from experts during the stakeholders meeting.

The process of identification and selection of the whole references is presented in Appendix 12.

The results of the pragmatic search allowed to select three kinds of references:

- Literature on general ethical principles in healthcare which can be applied to lung cancer screening;^{250, 255-257}



- Literature on lung cancer screening;^{251, 253, 254, 258-266}
- And literature specifically on ethical issues of lung cancer screening.^{252, 267}

7.2. Ethics in healthcare

7.2.1. *The four ethical principles of Beauchamps and Childress*

In healthcare, ethics play a central role: professionals are required to respect some ethical principles in the practice of their profession. The most widely known are the four ethical principles developed by Beauchamps and Childress:²⁵⁶

- *Principle of respect for autonomy*: involves respecting the ability of individuals to make informed decisions about their own lives and health. Healthcare professionals must respect patients' choices and involve them in the decision-making process.
- *Principle of beneficence*: encourages acting in the best interests of the patient, seeking to maximise benefits while minimising harm. The aim is to ensure patients' well-being and promote positive outcomes.
- *Principle of non-maleficence*: emphasises the obligation to do no harm and to minimise the risks associated with medical treatment.
- *Principle of justice*: emphasises the importance of distributing benefits and burdens fairly in society, including in healthcare. It aims to ensure equitable access to healthcare and to avoid all forms of discrimination.

These fundamental principles can also be applied to screening programmes and therefore to lung cancer screening.

7.2.2. *The four ethical principles applied to lung cancer screening*

In her doctoral thesis, Horeweg²⁵¹ applies the four ethical principles to lung cancer screening from the physician's perspective. However, the concept of ethics is polysemous²⁵⁶: depending on the chosen perspective (from the healthcare professional or the patient) ethical principles can be considered in different ways and potentially present a dilemma.

Table 93 presents the ethical principles of lung cancer screening from the healthcare professional's perspective (taken from Horeweg's thesis) and from the decision-maker's perspective, and the potential dilemma or challenge that may arise.


Table 93 – Beauchamp and Childress ethical principles applied to lung cancer screening and potential dilemma

Beauchamps and Childress ethical principles	Applied to lung cancer		Potential dilemma or challenge
	Healthcare professional (HCP) perspective	Policymaker (PM) perspective	
Beneficence/ Non-maleficence	HCP should propose lung cancer screening to targeted individuals for whom screening is most beneficial (benefits greater than risks). He should not offer lung cancer screening to those individuals in whom it is not beneficial or even harmful. Moreover, this principle also implies that physicians have the responsibility to minimise the harms of screening in whom screening is considered beneficial	PM should set up a lung cancer screening on a targeted population for whom screening is most beneficial (benefits greater than risks). PM should protect the population in whom the risks of screening outweigh the benefits, from getting screened (e.g., by providing transparent and accurate information to HCPs and participants).	Dilemma between beneficence/non-maleficence and autonomy: Well-informed individuals have the right to decide for themselves whether or not to undergo screening. And this can be conflicting with the principles of beneficence and non-maleficence in so far as an individual can decide to not participate in a screening programme due to fear of results or fear of the screening test
Autonomy	HCP should respect a person's decision to undergo lung cancer screening or not. As informed decision-making is a prerequisite for participation in screening, physicians also have the responsibility to inform screening candidates on benefits and harms of screening and give them time, room and support to make an informed screening decision.	In order to respect participants autonomy, PM should give all the useful information on benefits and harms of screening to let them make an informed decision.	The dilemma between justice and autonomy arises when it comes to finding a balance between "the individual's right to be screened" and "the PM's duty to allocate limited healthcare resources responsibly in order to maintain accessibility to healthcare". ²⁵¹ Other concern/dilemma: Inequality due to the selection of the eligible population (see below)
Justice	HCP have the responsibility to treat individuals, who are equal with respect to aspects relevant for screening, equally. This, for example, refers to providing care that is accessible and appropriate for the entire target population, or to the fair distribution of limited health care resources.	PM have the responsibility to ensure that screening programmes are equitable and accessible to all, and that they meet the needs of the entire population (target population or really the entire population?), regardless of socio-economic or geographical factors.	Challenge: Smokers are proportionately more numerous in the lower socio-economic strata of society and they generally participate less in preventive healthcare: how will the public decision-maker go about ensuring that the target population participates in the screening programme?

Abbreviations: HCP = Health care professional; PM: Policymaker; LDCT= Low-dose computed tomography



Linked to Beauchamp and Childness principles, other consideration can be raised:

Informed consent: Potential participants have the right to be informed about the consequences, benefits and harms of lung cancer screening. Presenting the information clearly and as simple as possible will be important to help them taking a decision.^{250, 258} The **lack of transparency about possible harms** is an ethical problem in screening programmes as it comes into direct conflict with the principle of autonomy and informed consent.

In her thesis, Pahwa²⁵² stated that '*normative and empirical research about cancer screening ethics has identified overdiagnosis as one of the most serious harms of screening, resulting in more harm than good due to overdefinition of disease and overdetection of disease*'; a statement that was retrieved in other publications.²⁵⁷ Overdiagnosis can lead to a disproportion, on the population level, between the real health benefits of early detection and the potential damage caused by unnecessary treatment, resulting in risks and negative consequences for the well-being of those screened. In addition, individuals who are over-diagnosed experience harm such as significant emotional stress, resulting from diagnostic anxiety, unnecessary medical procedures and even difficult treatment decisions. Overdiagnosis is difficult to understand and counterintuitive, as in clinical practice, overdiagnosed cancers cannot be differentiated from cancers that benefit from the screening programme through early diagnosis. People who were diagnosed with an early diagnosis through a screening programme may feel relieved and be convinced that screening 'saved their life', while they were actually were unnecessarily labelled as cancer patient and unnecessarily received treatment. The possibility of overdiagnosis and overtreatment should be clearly explained to people before they take part in a screening programme.

Another very common ethical issue in screening concerns **(in)equality of access**.²⁵⁸

- (In)equality of access due to geographical reasons (inaccessibility due to the remoteness of screening sites) or financial reasons (especially

downstream costs (diagnostic follow-up, monitoring, treatment, loss of income)), inequality of access to screening is an ethical problem.

- Inequality due to the selection of the eligible population:
 - screening programmes are by definition targeted programmes which are offered to the population considered to be most at risk of developing the cancer screened. Although this rationale is justified in particular by the benefit-risk balance, the principle of the autonomy of individuals who would like to be screened but are unable to do so because they are **not part of the target population** constitutes an ethical problem; some people can have a **feeling of injustice**;
 - inequality of access based on the socio-economic background of the specific target population for lung cancer screening: people who might benefit most from screening is the population that cannot be reached (or the hard-to-reach) and/or chooses not to participate for several reasons (see below).²⁵³ According to Aghlmandi et al.,²⁵⁹ attitudes vary among different demographic groups. For example, people from lower socioeconomic groups and minority ethnic groups are more likely to develop lung cancer (and to die from it) and more likely to have difficulty in accessing and adhering to screening, and demographics also affect attitudes to screening. Moreover, people from lower socioeconomic groups have more to lose with screening: the consequences from overdiagnoses are harder for them: financial costs, missed income.



7.3. Other ethical issues related to lung cancer screening

In contrast to long-running cancer screening programs such as breast, cervical and colorectal cancer screening, lung cancer screening raises specific issues related to the target population, the fear of stigmatisation and the smokers' behaviours.

7.3.1. Eligibility criteria for lung cancer screening

Defining the right target population for a screening programme is essential. In the case of lung cancer, this choice may raise ethical questions.

These eligibility criteria also raise questions of justice and equity.^{255, 267} For example, if screening is limited to smokers and ex-smokers, it could exclude other groups at greater risk than the general population, such as those at increased risk of lung cancer due to occupational exposure to hazardous particles such as asbestos, those who have never smoked but who have been heavily exposed to passive smoking, or those with a family history of lung cancer.^{259, 262} This can be overcome by the use of multivariable models that estimate lung cancer risk over a specified period and define a risk threshold to determine eligibility. Several of these risk prediction models for lung cancer incorporate family history of lung cancer, asbestos exposure, and other risk factors e.g., chronic obstructive pulmonary disease (COPD).²¹

7.3.2. Risk of stigmatisation

Social perceptions of cancer in general are often tinged with stigma, with cancer sufferers seen as weakened by the disease. In the case of lung cancer, this stigma can be reflected in the screening process, where individuals may be reluctant to undergo such an examination for fear of social judgement or the label of 'smoker' that may be attached to them.²⁶⁵

Studies have suggested that lung cancer screening may be experienced in a stigmatising way due to the focus on smoking-related behaviours. For example, research has shown that people screened for lung cancer may feel a sense of injustice, as they are often seen as responsible for their disease because of their smoking history, even though other factors may also play an important role in the development of the disease.²⁶²

Similarly, Aghlmandi et al.²⁵⁹ reported that stigma is also an important aspect of smokers' attitudes to lung cancer screening. A systematic review of 7 qualitative and 8 quantitative studies found that the general stigma attached to lung cancer also affects screening for the condition: "Patients reported feeling stigmatised by the prevailing view that if someone had lung cancer they would necessarily be a smoker and have inflicted this disease on themselves; and this view was seen by patients as unfair. Patients feared that they would be denied treatment and thought that lung cancer was neglected in research and screening because of the link between smoking and lung cancer."

Stigma can also lead doctors to delay the diagnosis of lung cancer, as they may think it is 'normal' for the patient to cough because he or she is a smoker.²⁵³

7.3.3. Risk of unethical behaviours

- In the context of lung cancer screening, some experts are concerned about the possibility that people who do not meet the eligibility criteria may resort to lying in order to take part. This issue arises particularly in relation to smoking history, where **lies may be generated for two distinct reasons**. Firstly, there are those who, fearing for their lung health, seek to reassure themselves by exaggerating their smoking behaviour. This group, often referred to as the '**worried well**', may be in relatively good health but are exaggerating their smoking habits in order to benefit from lung cancer screening. The second motivation stems from a feeling of shame, as individuals may play down their smoking history to **avoid the social stigma associated with lung cancer**.²⁵³ This dual dynamic of misinformation, whether motivated by health concerns or societal judgement, introduces a distortion into the process of selecting the appropriate target population for lung cancer screening and will affect the eventual balance of benefits and harms (those at higher risk will participate less resulting in a loss of benefit), those at lower risk will benefit more (more harm and also loss of benefit). Experts fear that the absence of objective criteria for selecting participants leaves individuals free to lie about their smoking habits, which could



undermine the accuracy and effectiveness of lung cancer screening programmes.

- Discussions have emerged around the concept of a '**licence to smoke**'.²⁵³ This concept implies that individuals may perceive participation in lung cancer screening programmes as a validation of their current smoking behaviour, on the assumption that early detection and potential treatment mitigate the associated risks. This raises ethical concerns about the unintended consequences of screening initiatives, which may reinforce smoking behaviour rather than encourage cessation. Ethical guidelines and interventions need to consider the delicate balance between encouraging participation in screening for early detection and conveying the importance of smoking cessation to safeguard overall public health.²⁶⁶ And especially as smoking cessation counseling only takes 1 minute and is effective (NNT 50 to obtain an additional quitter) and as smoking cessation has a higher impact on mortality than screening.

7.4. Discussion

7.4.1. *Is it ethical to implement a national cancer screening programme based on individual behaviour?*

Implementing a national cancer screening program based on individual behavior raises significant ethical considerations. While the aim is to target high-risk populations, this approach may inadvertently contribute to health disparities and stigmatization. Recent research, such as the work by Carter-Harris et al,²⁶³ underscores the ethical challenges associated with linking cancer screening programs to individual behaviors, particularly when addressing cancers related to lifestyle factors such as smoking. The potential for blaming individuals for their health outcomes and the risk of reinforcing societal biases should be carefully considered. Ethical guidelines, as emphasized by Juth et al,²⁵⁰ stress the importance of ensuring equity, autonomy, and informed consent in population-based screening programs. Striking a balance between the public health benefits of early detection and the ethical implications of singling out individuals based on

behavior is crucial for the successful and morally sound implementation of national cancer screening initiatives.

Recent research, including the work of Burzic et al.²⁶² highlights the need to carefully manage this tension, taking into account the ethical implications of balancing the wider public health benefits of early detection against the potential risks and burdens for individuals. Balancing the ethical considerations of individual autonomy and informed decision-making with the overarching goals of public health is essential to the development of effective and morally sound health policies for lung cancer screening. This ethical tension highlights the complexity of formulating policies that both address population-level health outcomes and respect the rights and preferences of individuals.

Finally, screening can give rise to concerns about privacy and confidentiality, since results can be interpreted as revealing personal health behaviors. This stigmatizing dimension of lung cancer screening underscores the importance of adopting a holistic approach that incorporates psychosocial and ethical considerations in the implementation of screening programs, in order to minimize the negative impact on the mental health and well-being of the individuals concerned.²⁶³

7.4.2. *How to reach the 'hard-to-reach'?*

The success and effectiveness of lung cancer screening programmes depend on the level of participation.²⁶² Indeed, if only a minority would participate, there will be no mortality reduction on the population level. As stated by van Hal et al,²⁵³ 'compared to the target groups for screening in the long-running cancer screening programs of breast, cervical and colorectal cancer, there are several additional obstacles regarding defining, locating and recruiting of the target group for lung cancer screening'. Emotional barriers (regret, guilt and feelings of entrapment, (anxiety, fear and the need to avoid lung cancer related information) are the main reasons justifying barriers to recruiting the target population.^{254, 261, 262}

Furthermore, recent research amongst others conducted by Burzic et al.²⁶² and van Hal et al.²⁵³ highlights the ethical complexities associated with disparities in screening uptake and the potential amplification of existing



health inequalities. These studies emphasise the need to take account of the social determinants of health and to adapt screening strategies to the specific needs of marginalised or underserved communities. Factors such as distrust of health systems, cultural diversity and limited health knowledge in 'hard-to-reach' populations pose ethical challenges that require culturally sensitive approaches and community engagement strategies. Reaching the 'hard-to-reach' populations is a pivotal challenge in the context of lung cancer screening, and recent research has delved into effective strategies to overcome this barrier. Studies, such as the work by Carter-Harris et al,²⁶⁴ emphasize the importance of targeted outreach and culturally tailored communication to engage populations that may face socio-economic, geographic, or cultural obstacles to screening participation. Implementing community-based interventions and leveraging technology can enhance accessibility for individuals in remote or underserved areas. Nonetheless, as highlighted by Burzic et al,²⁶² individuals in challenging-to-reach communities, especially those with lower socio-economic status, may be excluded from this technology due to the typical demographic characteristics of smartphone users: being younger, better educated, and having higher incomes.

7.5. Conclusion

Implementing a national lung cancer screening program in Belgium presents complex ethical considerations. Eligibility criteria, risk of stigmatisation, informed consent and transparency regarding possible harms such as overdiagnosis contribute to the ethical complexity. Unethical behaviour such as lying in order to participate in screening, and the concept of a "smoking permit" further complicate the ethical landscape. Strategies targeting 'hard-to-reach' populations highlight the ethical imperative of cultural sensitivity and collaboration to ensure equitable access. To meet these ethical challenges, clear communication, transparency and the protection of individual autonomy are paramount. Balancing public health objectives with ethical considerations is crucial when considering a Belgian lung cancer screening programme.

Key points

Implementing a national cancer screening program based on individual behaviour raises ethical dilemmas necessitating a delicate balance between public health benefits and individual benefits, harms, and autonomy. Lung cancer screening, unlike established programs for other cancers, introduces distinct ethical challenges tied to the target population, fear of stigmatization, and behaviours associated with smoking:

- defining the target population for lung cancer screening, poses questions of justice and equity, especially when eligibility criteria may inadvertently exclude high-risk groups beyond smokers and ex-smokers;
- stigmatization risk in lung cancer screening is significant, rooted in societal perceptions and the emphasis on smoking-related behaviors, potentially deterring individuals from undergoing screening due to fears of social judgment;
- potential unethical behaviors, such as lying about smoking history, motivated by health concerns or to escape social stigma, could introduce a distortion in the selection process for the appropriate screening population;
- reaching 'hard-to-reach' populations in lung cancer screening presents ethical complexities, demanding culturally sensitive approaches and community engagement to address disparities in screening uptake and ensure inclusivity.



8. OVERALL DISCUSSION

Lung cancer, one of the most frequent cancers in Belgium, is a disease with a poor prognosis, to a large extent because the majority of tumours are diagnosed at an advanced stage. Early-stage lung cancer has a much better prognosis, hence early detection through screening for asymptomatic disease could be considered as a worthwhile approach to reduce disease burden and mortality related to lung cancer. When a screening programme is considered as possibly appropriate, a next step before implementation is an in-depth review of the evidence for effectiveness and cost-effectiveness.⁹

This report provides an evidence overview of the potential benefits and harms associated with lung cancer screening, together with a cost-effectiveness analysis based on Belgian cost information. Results on the clinical effectiveness and harms of lung cancer screening were mainly based on the results of three systematic reviews with good methodological quality: a Cochrane review (2022),⁵¹ a EUnetHTA report (2020),⁴⁹ and an evidence review from the US Preventive Services Task Force (USPTF) (2021).⁵⁰

8.1. Benefits and harms of lung cancer screening

8.1.1. Benefits: reduced mortality

Comparing all-cause mortality in individuals who underwent screening with those who did not is the key determinant when assessing the efficacy of cancer screening programmes, as it directly addresses the fundamental question whether such programmes save lives. All-cause mortality avoids the potential biases in determination of the cause of death while lung-cancer related mortality is prone to detection bias, which has been shown to be a concern in several of the included studies (see Figure 11). All-cause mortality includes the rare but possible deaths resulting from a false positive screening result, covers early or late complications of treatment that may lead to death (which may not always be registered as lung cancer mortality), as well as the (beneficial or harmful) effect on mortality resulting from diagnosis and treatment of incidental findings. For these reasons, and if there is sufficient evidence of good quality available for all-cause mortality, we consider this to be the most reliable and important outcome to evaluate

the effectiveness of a cancer screening programme from a public health perspective. However, as only a low percentage of individuals within a screening trial will die from the cancer for which is being screened, these trials require substantial participation numbers to demonstrate a statistically significant reduction in all-cause mortality. Among the identified trials for lung cancer screening, only the US National Lung Cancer Screening Trial (NLST) showed a significant reduction in all-cause mortality, which is supported by the direction and the absolute changes in all-cause mortality from most other, smaller trials. Combining data from multiple randomised screening trials to provide an effect estimate with adequate statistical power shows that screening individuals at high risk of lung cancer with low dose CT scan **reduces all-cause mortality with 5%** (RR 0.95, 95% CI 0.91 to 0.99). To prevent one death from all-cause mortality, it is estimated that 210 people would need to undergo screening. Regarding cancer-specific mortality, the evidence shows a **21% reduction in lung cancer-related mortality** (RR 0.79, 95% CI 0.72 to 0.87).⁵¹ The trials also consistently demonstrate a persistent decrease in stage IV lung cancer cases. In summary, the evidence supports lung cancer screening is effective in reducing both lung cancer-specific mortality and all-cause mortality, by identifying individuals at an earlier stage of disease when treatment is more effective.

8.1.2. Harms: false positives, overdiagnosis, radiation exposure, and incidental findings

It is unequivocal that some participants experience harm from lung cancer screening, as is the case in all existing cancer screening programmes. However, there remain uncertainties in the available evidence regarding the extent of potential harms resulting from lung cancer screening.



8.1.2.1. False positive and false negative results

Screening for lung cancer with LDCT may lead to harm due to the consequences of false positive screening results. While a majority of the trials reported false positive rates, only a few provided information on subsequent unnecessary tests and invasive procedures, with even fewer reporting adverse events related to false positive evaluations. Moreover, trials differed in thresholds for positive screens and the categories of diagnostic and therapeutic interventions, posing challenges in result interpretation. Consequently, a range (minimum, maximum) is presented rather than a mean to quantify these outcomes. Across the included trials, **false positive rates varied largely** ranging from 8% to 46% in the initial screening round and decreased with subsequent screening rounds.^{bb} This resulted in invasive procedures for false positive findings in 0.1% to 1.7% of the participants, with only a few trials reporting complications associated with these procedures.

The trials observed only a small number of false negative results, suggesting that the consequences of these results (e.g., false reassurance) are likely to be limited.

8.1.2.2. Overdiagnosis

Overdiagnosis is the detection of cancers that would never have been found or never would have caused harm, were it not for the screening test.⁴⁰ Overdiagnosis is not identifiable at the individual level (we cannot tell whether a diagnosed person is overdiagnosed or not), and is difficult to quantify precisely at the population level. Nevertheless, it is one of the most important harms associated with cancer screening and should be carefully assessed in both benefit-harm balancing and cost-effectiveness analysis. As with the results for false positives, the overdiagnosis estimates varied so much between studies that there is uncertainty around the overall estimate. **Overdiagnosis estimates range from 0% to 67% of screening-detected**

cancers across individual LDCT trials. In other words, between zero and two thirds of the screen-detected cancers may have been overdiagnosed within the trials. It has been suggested that variations in overdiagnosis estimates depend on many factors, such as on duration of follow-up,⁶⁴ on the screened population, on differences in nodule management, whether data from the follow-up period is accurate, and whether participants in the control group have received screening (contamination).^{50, 73}

8.1.2.3. Radiation exposure

It is crucial to take into account the radiation-related risk, given that only a fraction of screening participants will benefit from the examinations, while all participants will be exposed to the risks associated with the ionizing radiation from LDCT. As only few included trials estimated cumulative radiation exposure for screened participants, the risk of radiation-induced cancers was retrieved from modelling studies. The German Federal Office for Radiation Protection published conservative estimates of the lifetime attributable cancer risks resulting from repeated LDCT screening tests for a German population of heavy smokers or ex-smokers, considered representative for a Western European population. Considering a screening scenario with annual LDCT screening of (ex-) smokers aged between 50 and 75 years, the **estimated radiation-related lifetime attributable risk to develop cancer is below 0.25% for women** (2.5 per 1000) and **about 0.1% for men** (1 per 1000).¹⁰¹ It should be noted that the risk for radiation-induced (lung) cancer is significantly higher for women than for men.

Furthermore, before medical radiological procedures (such as a LDCT scan) can be conducted as part of a population screening programme, a justification study must be performed according to the model and modalities determined by the Federal Agency for Nuclear Control (FANC), the regulatory body for nuclear safety and radiation protection in Belgium, as stipulated in the Belgian Royal Decree of 13 February 2020 on the medical

^{bb} As mentioned before, we considered both indeterminate or suspicious lung nodules, which eventually turn out not to be malign, to be false positive screening results.



exposures and exposures in non-medical imaging with medical radiological equipment.¹¹⁰

8.1.2.4. *Incidental findings*

In contrast to cancer screening programmes that focus on specific organ systems, such as cervical cancer screening through cytology or HPV testing and mammography screening for breast cancer, LDCT screening of the lungs captures images of the entire chest region. This inherently reveals incidental findings which are unrelated to the purpose of screening. These findings are frequently reported in different organ locations and may cause benefit or harm the participant, while their management adds costs and workload to the health care system. As an example, incidental findings detection may be associated with the early diagnosis of another life-altering condition (e.g., extrapulmonary cancers, beneficial to a participant if early detection leads to a better outcome); however, other incidental findings may cause unnecessary work-up and may lead to morbidity and thus be harmful to a participant (e.g., a liver biopsy for a lesion which is ultimately determined to be benign).

The prevalence of incidental findings varied among the included trials, but there was no standard definition for what qualifies as an incidental finding and often, it was unclear whether these findings were deemed clinically significant or actionable. In one of the expert meetings,^{cc} there was extensive debate about incidental findings, and it was considered as likely to be a key factor in overall effectiveness and cost-effectiveness of a lung cancer screening programme. Furthermore, in contrast to the trials that were conducted several years ago, and in which the significance of incidental findings was at the radiologist's discretion, some more recent (pilot) studies include specific protocols and guidelines on the management of incidental findings.^{76, 268} These protocolised approaches to reporting and managing incidental findings have only recently been developed, and aim to minimise the harms from incidental findings and increase the cost-effectiveness of a

screening programme. During the expert meeting, the European Respiratory Society (ERS) Statement on the Management of Incidental Findings was shared, which identified 23 categories of incidental findings along with recommendations on the optimal approaches for their reporting and management.²⁹ We performed an exploratory analysis to estimate the prevalence of incidental findings for which an additional examination is recommended according to the ERS Statement. In summary, our estimation suggests that **approximately 23% of screening participants would require an additional examination for incidental findings**. This estimation largely depends on two of the most commonly occurring incidental findings, namely coronary artery calcification and emphysema. These may provide an opportunity to assess for cardiovascular disease and COPD, respectively, and their assessment could allow early preventive treatment like statin therapy, or smoking cessation. This, in turn, could alter the balance of benefits and harms of screening for participants.²⁰ However, it has to be noted that the overall benefit achieved by treating asymptomatic disease is currently unknown.²⁶⁹

Further research needs to be done in order to quantify the health gains or losses of incidental findings associated with a lung cancer screening programme, but it is clear that an important proportion of the screening participants may need additional examinations, which may result in additional morbidity and impact their quality of life. It is important that participants should be informed appropriately prior to participating in screening. Finally, protocolised approaches to the reporting and management of incidental findings are proposed for systematic assessment and standardised onward management in primary and/or secondary care,⁷⁶ which will have a direct impact on their workload.

^{cc} Preliminary results of the literature review on (cost-)effectiveness of lung cancer screening and the proposed methodology of the Belgian cost-effectiveness analysis were shared with a group of experts with specific

expertise in cancer screening and/or lung cancer, and including different medical specialties (e.g., pulmonologist, radiologist, radiotherapist) as well as general practitioners (see the colophon).



8.1.3. Quality of the evidence

Evidence for the benefit of lung cancer screening from randomised trials was identified through a systematic search of the medical literature. Randomised controlled trials can overcome several biases of observational data such as lead time bias, length time bias and bias related to overdiagnosis. The quality of the included RCTs was fair to good for the majority of included trials. This leads to a moderate level of evidence according to GRADE for important outcomes such as overall mortality, lung-cancer specific mortality, and the reduction in the number of tumours that are metastatic at diagnosis. However, for possible harms the quality of the level of evidence is low according to GRADE. For example, the degree of overdiagnosis is difficult to quantify accurately, even in trials with sufficiently long follow-up to cover lead time, as essential information on contamination is missing. Also, the degree of the impact of screening and screening results on quality of life remains uncertain, as few trials report usable data on QoL. Overall, we conclude that **the level of evidence for lung cancer screening is moderate for the benefits and low for the harms.**

8.1.4. Balancing benefits and harms and informed choice

Overall, trying to balance the benefits and harms of LDCT screening would likely result in significant variability in decisions regarding participation, after being fully informed about all possible benefits and harms of the screening programme. It will therefore be important to provide complete and clear information to all potential participants. This may result in lower participation rates, but for ethical and fairness reasons, it would not be justified to withhold information on potential harms to potential participants.²⁵³ Information and consent forms should be accessible to everyone, including the socio-economic more vulnerable to ensure the programme has no negative impact on health equity.

A frequently used method for presenting the expected benefits and harms, along with relevant contextual information that may be beneficial for individuals seeking information on lung cancer screening, is through the use of a 1000-person tool. Examples of these include the infographic from the International Agency for Research on Cancer (IARC),²⁷⁰ or the tool from the Canadian Task Force on Preventive Health Care.²⁷¹ Because such a tool illustrates the balance between the potential for harm and the potential for benefit, there is no “correct” choice to be taken, but individuals are encouraged to decide for themselves to make informed choices regarding screening based on the available evidence and on what matters most to them.²⁷¹ A similar graph based on the results of this health economic evaluation is presented later in this chapter.

8.2. Systematic literature review of economic evidence

8.2.1. Methodological characteristics and shortcomings of selected studies

A systematic literature search was performed for economic evaluations of lung cancer screening. Twenty-three primary economic evaluations published since 2020 were retained in our overview. As no economic evaluation for the Belgian context could be retrieved, the studies were analysed to identify their methodological approaches, inputs and shortcomings as sources of inspiration for our own model.

First, the selected studies generally attributed insufficient attention to the **selection and invitation of the screen-eligible population**, which is considered one of the main organizational difficulties related to a lung cancer screening programme due to a lack of individual data on the smoking history of the Belgian population.

- While most studies used categorical eligibility criteria (20/23)^{dd} consisting of age and smoking history, only a handful of studies (4/23)

^{dd} Numbers between brackets indicate the number of studies relative to the total number of identified studies. For the references and a broader discussion of

the individual studies, we refer to the systematic review on the cost-effectiveness in Chapter 4.



used the exact same **eligibility criteria** as the leading trials (i.e., NLST and NELSON) on which the majority of the analyses are based.

- While approximately half of the studies (11/23) opted for the **age eligibility criteria** of either NLST (55-74) or NELSON (50-74), a considerable number of studies (12/23) deviated from these age windows, often without a clear evidence base. Studies increasing the stop age generally found LCS to be less cost-effective with, among others, lower additional health benefits due to a substantial increase in the number of overdiagnosed patients. Studies decreasing the start age generally concluded that LCS became less cost-effective due to the relation between age and lung cancer incidence.
- Of the studies opting for categorical criteria, the **smoking history eligibility criteria** of the NLST trial (i.e., individuals with 30 pack years who are currently smoking or who stopped smoking in the past 15 years) are most often opted for (8/23). While a considerable number of studies is based on the evidence of the NELSON trial, the smoking history eligibility criteria of NELSON are rarely used (3/23) to define the screen-eligible population. To date, the impact of expanding or narrowing the smoking history requirements remains unclear due to a lack of high-quality evidence.
- A minority of studies (3/23) defined the eligibility for LCS using a **risk assessment tool**, which calculates an individual's risk of developing lung cancer over a specific period based on multiple inputs (e.g., smoking history, age, sex, etc.). When using a risk assessment tool, an individual is eligible for screening when the individual risk is above a pre-specified risk threshold. The limited number of studies examining the added value in terms of cost-effectiveness of these tools show promising results. However, ongoing trials (e.g., 4-IN-THE-LUNG-RUN) will generate more evidence in the future to incorporate in health economic evaluations.
- Surprisingly, and identified as one of the major shortcomings in the body of evidence, only less than half of the selected studies (9/23) described **the means of identifying and inviting the screen-eligible**

population and took a cost for this element into account in their models. The remaining studies either downsized the cost of a screening programme to an LDCT scan or did not provide sufficient transparency on which costs were taken into account in relation to the organization of the examined screening programme. Not taking into account a cost for identifying and inviting screen-eligible candidates leads to a potentially substantial underestimation of the costs of the LCS programme and would incorrectly lead to more favourable results in terms of cost-effectiveness. Incorporating a cost for this element is ultimately important as the cost associated with the organization of the LCS programme is shown to have a substantial impact on the cost-effectiveness in the sensitivity analyses. Some studies incorporated the cost of identifying and inviting the screen-eligible population of other, existing screening programmes. While this approach is superior to not taking into account a cost for this element, it should be noted that this cost in the case of lung cancer screening could, depending on the implementation, be considerably higher due to the lack of data on individual smoking history in government databases or GP records. This means that a broader population than the screen-eligible population will have to be contacted to collect this information.

- Related to the abovementioned element, the majority of studies (13/23) either explicitly or implicitly assumed an unrealistic **participation rate** of 100%. This approach leads to a more optimistic, but incorrect, estimate of the cost-effectiveness of LCS due to not taking into account non-participants for which costs of identification and invitation were made but no screening-related health benefits (and potential cost savings in treatment of LC) will arise. Currently, the existing screening programmes for colorectal cancer, cervix cancer, and breast cancer reached a coverage of approximately 65% in 2022 in Flanders.²⁷² Screening coverage data for the Brussels region ranges between 28% for colorectal cancer screening and 53% for breast cancer screening (2020).²⁷³ For the Walloon region, recent data on cancer screening coverage is not publicly available. Similarly, only five studies took into account an adherence rate of less than 100% in subsequent screening rounds.



Second, the selected studies used a variety of different **screening intervals** including a single screening round, annual, biennial, triennial screening or trial-specific intervals. The studies most often evaluated annual screening (16/23) followed by biennial screening (9/23). For the annual screening interval, studies most often use the evidence of the three annual screens performed in the NLST trial by extrapolating costs and effects beyond these three consecutive annual screens conducted in the trial. A selection of studies examining annual versus biennial screening (3 studies) as well as the published HTAs and systematic reviews argue biennial screening to be more cost-effective than annual screening. Remarkably, and possibly as a consequence of the lack of large trial evidence on biennial versus annual LCS, three other studies in our selection concluded annual screening to be more cost-effective than biennial screening. This means that moving from biennial to annual screening would result in a proportionally larger increase in incremental effects than in incremental costs. This seems rather counter-intuitive. Interestingly, while most studies base the clinical effectiveness in their models on NLST or NELSON, only a small minority of studies used the exact screening intervals of these trials.

Third, a specific set of **screening-related factors** were identified which should be addressed in any economic evaluation of a lung cancer screening programme to obtain a reliable estimation of the cost-effectiveness of LCS:

- One of the major harms of LCS was identified to be **overdiagnosis** (see Chapter 3.2.9). Unfortunately, less than half of the selected studies (11/23) accounted for overdiagnosis in their models, potentially leading to an overly optimistic ICER due to a substantial amount of costs (due to unnecessarily performed procedures) not leading to health benefits compared to a situation without screening. Not incorporating overdiagnosis in health economic models is therefore considered to be a major shortcoming, especially as the few studies varying overdiagnosis rates find a substantial impact on the ICER. Reported non-zero overdiagnosis rates ranged between 1.9% and 31%. Seemingly overdiagnosis posed some methodological challenges as the handling of overdiagnosis differed greatly between studies and many lack transparency on how overdiagnosis was addressed in their models.
- Most studies (17/23) did not disclose how the **false negatives** were handled in their model. However, it is important to note that studies which did not incorporate false negatives explicitly in their models, possibly do take false negatives into account implicitly as false negatives can be detected in an upcoming screening round or are included in the group of interval cancers.
- The same phenomenon seems to be present with regard to the **specificity** and handling of **false positives** in the selected studies. Only a handful of studies (6/23) reported how they incorporated the impact of false positives in their model. Three studies solely assigned a cost to false positive cases due to the unnecessarily performed diagnostic procedures following a false positive LDCT scan. Three other studies additionally assigned a temporary disutility to false positives due to increased anxiety levels as a consequence of a (false) positive screening result. Specificity was varied in the sensitivity analyses by half of the studies, of which two found a substantial impact on the ICER. Due to the lack of transparency of the selected studies, there is a great deal of uncertainty around the impact of specificity and false positives, but systematic reviews argue the impact could be substantial and should therefore be addressed in future health economic evaluations.^{111, 113}
- Two sources of bias specifically linked to screening (i.e., lead-time & length bias) potentially distort the results if they are present in the data on which the models are based without being corrected for. Only a handful of studies (6/23) reported accounting for **lead-time bias** in their models using lead times between 0.5 and 2 years. In two systematic reviews on the cost-effectiveness of LCS, the lead times considered in the selected health economic evaluations even range up to 8 years.^{113, 114} The lead time was varied in the sensitivity analyses by only three studies, which concluded the impact on the ICER to be moderate to substantial. The systematic review of Grover et al.¹¹³ argues the impact of lead-time bias is minimal. Length bias was considered by only two studies. In the presence of **length bias**, originating from screening programmes mostly detecting the slower progressing nodules, the effectiveness of LCS might be overestimated. However, the impact of (not) taking into account length bias is at the moment unclear.



- Screening can lead to a positive, negative or **indeterminate result**. Indeterminate results require further (diagnostic) testing and may therefore increase costs as well as worsen health outcomes due to potential adverse events associated with these additional procedures and potentially increased anxiety levels. Only a handful of studies (5/23) accounted for indeterminate results in their models, of which two assigned a temporary disutility and a cost for follow-up to these indeterminate cases. The remaining studies opted to only include an additional cost or a temporary disutility. None of the selected studies varied the cost and/or disutilities related to indeterminate results. However, the systematic review of Grover et al.¹¹³ and the HTA of AIHTA¹¹¹ argue the magnitude of the disutility assigned to indeterminates has a substantial impact on the ICER.
- **Incidental findings** may require a referral to other physicians and subsequently a suitable treatment. None of the selected studies take into account both the costs of treating these incidental findings and the effects on health resulting from these treatments. Therefore, the impact of incidental findings on the ICER remains unclear both in terms of direction and magnitude. Depending on the protocols for handling incidental findings, the impact on the cost-effectiveness of LCS could be substantial.¹¹¹ For a full discussion of incidental findings within LCS, we refer to Chapter 3.2.10.

8.2.2. Results of selected economic evaluations

All included studies concluded that lung cancer screening imposes **additional costs on the health care system as well as health benefits** in terms of LYG or QALYs gained compared to the usual care without lung cancer screening. This general trend of LCS being both more costly and more effective is also confirmed by the selected systematic reviews and HTAs, meaning that with a high level of certainty LCS is located in the north-east quadrant of the cost-effectiveness plane.^{111, 113, 114} The **ICERs in the selected studies vary greatly** between £1529 (~€1772)/QALY gained and CA\$92 025 (~€63 269)/QALY gained in the base case analyses. As LCS is located in the north-east quadrant of the cost-effectiveness plane, studies compare the ICER to a willingness-to-pay threshold to conclude whether the

LCS programme is cost-effective. With the exception of e.g., NICE, these thresholds are usually not defined in the national guidelines on health economic evaluations. While it should be noted that there was considerable variation in the thresholds used by the various authors and there were substantial methodological shortcomings (see above), almost all identified studies concluded lung cancer screening is likely cost-effective compared to a situation without lung cancer screening. In contrast, two studies concluded that LCS is unlikely to be cost-effective.

A selection of studies (4/23) examined whether including a **smoking cessation intervention** within a lung cancer screening programme is cost-effective.^{129, 132, 133, 138} Within this selection of studies, all authors concluded that LCS with smoking cessation intervention is more cost-effective than LCS without smoking cessation intervention. This means that LCS without smoking cessation intervention can be considered to be an extendedly dominated strategy.

8.2.3. Conclusion

While a substantial number of studies examining the cost-effectiveness of lung cancer screening were published over the past four years, the majority of these studies suffers from considerable methodological shortcomings which could lead to overoptimistic estimations of the cost-effectiveness of lung cancer screening. Due to these shortcomings as well as the absence of an evaluation for the Belgian context, we argue that, based on the systematic review carried out above, it is not possible to provide a reliable evidence-based recommendation on the cost-effectiveness of lung cancer screening in a Belgian context. We thus conclude that a primary health economic evaluation of LCS for the Belgian context is necessary to answer this research question.



8.3. Belgian cost-effectiveness analysis

8.3.1. Methodology

8.3.1.1. Modelling approach

For this health economic evaluation, the cost-effectiveness of LDCT screening in an adult high-risk population is compared to no screening (i.e., the current Belgian situation). The rationale of cancer screening is to detect cancers when they are at an early, curable stage of their development, before they may have progressed into advanced, incurable cancer. Within our model, we applied the LDCT screening performance and the stage shift reported by the NELSON trial (see Box 3) on overall survival and cost data of Belgian lung cancer patients. The model took into account the lung cancer stage at diagnosis, the histology (NSCLC vs SCLC), and the age group eligible to LDCT screening (50-75y). The results of the economic evaluation are expressed in incremental costs, incremental effects, incremental costs per life-year gained and **incremental costs per quality-adjusted life year gained**. The model starts with the invitation of the target population, reflects the LDCT screening results (including negative, indeterminate and positive findings), includes consequences from both true and false-positive findings, and overdiagnosis. The number of life years gained was modelled through the stage shift and QoL data was extracted from the literature. The health economic evaluation started using a base case scenario, that is a scenario following results of the NELSON trial. Alternative scenarios were developed in which key effectiveness (e.g. overdiagnosis) and cost variables were modified.

Box 3 – The NELSON trial

Based on the evidence presented in the clinical part of this report, we chose to determine the cost-effectiveness based on the results of the Dutch-Belgian^{ee} Randomized Lung Cancer Screening Trial (NELSON) (RCT-based modelling). This trial is the second largest (finished) trial after NLST (which is of importance for the robustness of the model). No lung cancer screening was done in the control group of the NELSON trial whereas CXR screening was offered to the control group of the NLST. The NELSON trial minimized false positive LDCT screening results via the volumetric nodule management and the introduction of a third "indeterminate" LDCT screening test, resulting in a specificity greater than in the NLST. Furthermore, details on false positive evaluations and complications were published for the initial three screening rounds.⁷¹

Main methodological concerns include the change in assessing lung cancer-related death - from using a death review panel to relying solely on death certificates, which implied unblinded assessment of causes of death. A fourth screening round with a 2.5-year interval was added after the trial commenced. Women were underrepresented, constituting only 16% of participants. Originally, the study focused only on the inclusion of male study participants, a small subset of women was approached in the second recruitment. Published results from the NELSON trial primarily focus on men.¹⁰ We obtained additional information on test performance and mortality data for both sexes from the NELSON investigators. Data regarding incidental findings were collected only for a subset of male participants.⁸³ While an important drop in the overdiagnosis estimate for males has been observed at the extended follow-up of the NELSON trial (from 19.7% at 4.5 years after the final screen to 8.9% at 5.5 years), the contamination rate^{ff} was determined only for a sample of male subjects at baseline and not during the entire follow-up of the trial. The estimated overdiagnosis rate for women at 4.5 years after the final screening was

^{ee} Approximately six percent of the participants in the trial were Belgian.²²⁴

^{ff} Defined as the proportion of the control group who have been screened, the higher the contamination rate, the more the estimate of overdiagnosis is biased towards the null.⁷³



45% (unpublished data). The combined (unpublished) data for men and women together resulted in an overdiagnosis of 23.9% at 4.5 years after the final screen, which was used in our base case scenario. Although the NELSON trial authors state that an overdiagnosis rate of 8.9% may be considered as the upper limit of overdiagnosis in the trial,¹⁰ we believe that caution is needed when interpreting these results on overdiagnosis. In our analysis, we complemented the base case scenario with scenarios including different overdiagnosis rates to account for the existing uncertainty surrounding overdiagnosis.

Finally, the NELSON trial showed a significant decrease in the risk of lung cancer-related mortality (RR 0.75; CI 0.62-0.90), and there was no significant reduction in the risk of all-cause mortality (RR 0.98; CI 0.90-1.07).⁵¹

Our methodology involves calculating the life years gained through stage shift, after excluding the overdiagnosis for which there is no beneficial effect. Within our model, lung cancers in the intervention and comparator group are linked to costs and effects (overall survival and QoL) in a Markov model:

- **Participants without cancer:** We only modelled the impact on QoL and costs of indeterminate and false positive findings. The NELSON trial reported no death in subjects operated for non-cancerous disease in the LCDT-screening group.⁷¹ Therefore, no related effects were included in our model.
- **Interval cancers** were assumed to be diagnosed at the same time and at the same stage as if there was no screening. No incremental differences were modelled for these cancers.
- **Overdiagnosed cancers:** Overall survival of lung cancer patients is a biased outcome when substantial overdiagnosis is present. As overdiagnosed cancers do not lead to any survival benefit, only costs

were included for these cancers in the model. Alternative scenarios applying different overdiagnosis estimates were evaluated. Costs of overdiagnosed cancers were those related to stage I NSCL cancers. As the costs of all screening-detected cancers are included in the model (sum of both the overdiagnosed and non-overdiagnosed cancers), this does not bias incremental cost estimates.

- **Non-overdiagnosed cancers** in the LDCT screened group: differences in overall survival, QoL and costs due to stage shift as compared to the comparison group were modelled.

The results of the model reflect the evidence from NELSON regarding the number of screen-detected cancers and interval cancers in the lung cancer screening group, the number of cancers in the control group, the percentage and number of overdiagnosis, as well as the stage and histology distribution in the lung cancer screening group (per screening round) and the lung cancer stages in the control group.

To **validate** our model, we compared the modelled life years gained through the stage shift versus the impact on all-cause mortality if the hazard ratio⁹⁹ for all-cause mortality from the meta-analysis was applied to the Kaplan-Meier survival curve of the control arm from the NELSON trial (information received from the NELSON investigators). Although this approach has limitations (e.g., because it assumes a constant hazard ratio over time), this check was viewed as relevant and useful.

We used survival and cost data of a large sample of Belgian lung cancer patients (incidence year 2015-2020, n = 27 421) from the relevant age group (between 50 and 75 years), with data stratified according to stage and histology (NSCLC vs SCLC). The BCR data include nearly all cancer cases in Belgium, with nearly complete information on the stage of the disease at time of diagnosis, as well as on histological subtypes. Individuals with WHO performance status 4 were excluded from the database as they would not be considered eligible for screening. Individuals with a previous (lung)

⁹⁹ Limitation: The all-cause mortality results from the meta-analysis are presented as risk ratio (RR), since only a few trials reported the hazard ratios (HRs)⁵¹



cancer diagnosis were excluded. Lung cancer survival curves stratified by **smoking status** or smoking history were not available, as data on smoking (history) from the Belgian population is not available at the individual level in any database. It is difficult to estimate the possible effect this limitation has on the (cost-) effectiveness outcome in our model.^{hh} Furthermore, the Belgian data represent substantially more **symptomatic disease** than would be the case in screen-detected cancers, which are per definition asymptomatic.

Considering all these factors, we view the utilization of these data as one of the primary strengths of this Belgian health economic evaluation, reflecting recent and real-world survival data of lung cancer patients.

8.3.1.2. Inputs for QoL

Lung cancer screening can have both positive (i.e., QoL gain due to stage shift) and negative effects on QoL (e.g., false positive or indeterminate results). While QoL should therefore be considered as a relevant endpoint in clinical trials, the evidence on QoL resulting from the identified trials is incomplete. QoL data of NELSON was therefore supplemented with QoL information obtained using a targeted (non-systematic) search strategy for reviews on QoL in lung cancer patients and QoL information identified in the economic literature review. Due to shortcomings of the recently published literature (see Section 0), the utility values obtained by Tramontano et al.¹⁹⁶ were used in the base case analysis. While the study of Blom et al.²⁰⁸ suffers from a major limitation (i.e., heterogeneity in selected studies), the stage utilities of this meta-analysis were used in one scenario analysis. The model also incorporated disutilities in the case of indeterminate and false positive results based on evidence from the NELSON trial. More specifically, a disutility of 0.0307 was assigned to indeterminates and false positives for 3 months. In a scenario analysis, a higher disutility (0.063) resulting from the economic literature review was applied.

^{hh} It is plausible that the sample included fewer heavy (former) smokers compared to a screening-eligible population based primarily on smoking

As participation in lung cancer screening would be voluntary, we assume no disutility for participation in lung cancer screening. In addition, due to a lack of evidence on the magnitude and duration of QoL loss associated with overdiagnosis and lead time, the base case does not incorporate disutilities, nor QoL gains, for these aspects. Including a disutility would disfavour the intervention's cost-effectiveness. Vice versa, if the difference in quality of life between stage I and IV lung cancer is larger than observed in the study by Tramontano et al.¹⁹⁶ this would be in favour of the intervention's cost-effectiveness. The combined impact of this potential under- and overestimation is unclear.

8.3.1.3. Inputs for costs

Cost data related to the identification and invitation of potential screen-eligible candidates was provided by the Flanders Department of Care based on their experience and cost information of existing screening programmes and was checked by an expert from the relevant departments of the other regions. This information was then applied to a potential invitation procedure for LDCT screening. Cost information related to the LDCT scans is based on the 2024 nomenclature (which does not make a distinction between normal and low-dose CT). As one of the major strengths of this economic evaluation, costs related to the diagnosis and treatment of lung cancer were based on real-world Belgian data obtained from BCR- IMA – AIM data. This data was supplemented with cost information of the NELSON trial (e.g., procedures performed for false positive and indeterminate results) and translated to costs using the Belgian nomenclature. Costs were included as exhaustively as possible, but costs related to complications of treatment could not be fully identified in the administrative data due to lack of specificity.

The analysis was conducted from a health care payer perspective. This does not include transport or productivity costs. Extending the perspective to a societal perspective would include these costs. If the stage shift resulted in

history. As smoking increases the competing risk of cardiovascular events, this could lead to an overestimated survival benefit through stage shift within the model.



less productivity loss than if the cancer had been symptomatic, this would have a positive impact on the cost-effectiveness of lung cancer screening. On the other hand, there is the time commitment for screening participation. If this is not done during free time and participants report sick to undergo further investigations after e.g., an indeterminate or false positive finding, this will have a negative impact on productivity and negatively affect the ICER for lung cancer screening from a societal perspective.

8.3.2. Results

8.3.2.1. Base case and 1000-person figure

The economic model assumed, based on the best available evidence, for the base case: participation rate as in the NELSON trial (51.1% of eligible and invited persons), a lifelong time horizon applying discount rates of 3% for costs and 1.5% for effects, overdiagnosis of 23.87%, stage utilities of Tramontano et al.¹⁹⁶ and a 40% price discount on systemic therapy (see Box 4). The base case analysis shows lung cancer screening would result in an incremental cost of €77 747/100 participants and 4.64 QALYs gained/100 participants, which translates into an ICER of €18 530/QALY gained compared to no LCS. The cost-effectiveness acceptability curve indicates that LCS has a 1.5%, 72% and 94% probability of being cost-effective at a willingness to pay threshold of €10 000, €20 000 or €30 000 per QALY gained, respectively (Figure 34).

Box 4 – Managed entry agreements (MEA) and price discounts

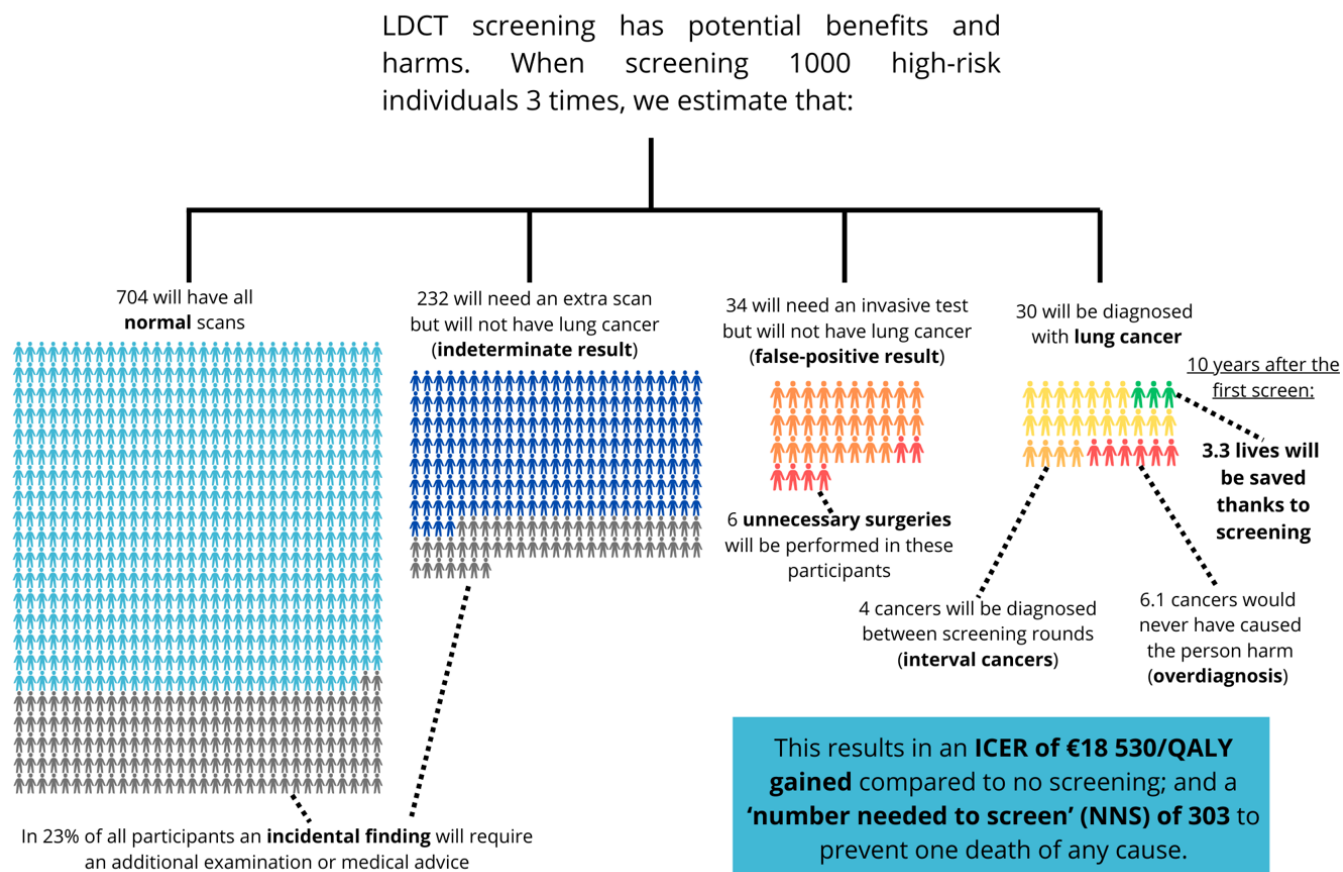
Many cancer drugs (ATC class L drugs: antineoplastic and immunomodulating agents) are subject to managed entry agreements (MEA), to share the risks and uncertainties arising from public coverage of pharmaceuticals, whose (cost-)effectiveness is still unknown or for which the budget impact is expected to be very high, but for which early access for the patient is wanted.^{274, 275} Within the systemic therapies used for treatment of lung cancer, several are reimbursed in such a MEA in which confidential price discounts are negotiated between the company and the government. Due to this confidentiality, we cannot include the

exact price discounts. Nevertheless, the MORSE report (Monitoring of Reimbursement Significant Expenses) report²⁴⁵ provides insight into the average discount given in a specific year for all products reimbursed under a MEA and thus reflects the best publicly available evidence. Whereas the discount in 2021 was >50% on average, in 2020 it was 40% on average (2017: 25.5%; 2018: 27.2%; 2019: 39.4%; 2020: 40.4%; 2021: 53.8%).²⁴⁵

As the applied average price discount remains an informed guess about the actual average price discount related to the products in our analysis, we presented the result for 40% as the base case; and the results in scenario analyses for 0%, 10%, 20%, 30%, 50%, 60%, 70%, 80% and 90% discounts. As such, the policymaker who is aware of the actual price discount for individual products can determine which ICERs best reflect reality.

The expected benefits and harms of LDCT screening from the base case of this health economic evaluation are presented in Figure 37. Participants are offered three LDCT screens (year 0, 1 and 3) with a total follow up of 10 years after the initial screen. We were able to classify participants into mutually exclusive groups based on information from the first three rounds of the NELSON trial from Horeweg et al.²³⁴, indicating that 70.4% of the screened participants had **exclusively negative screen results**, and 6.0% of the participants had at least one positive screening result. The remaining 23.6% of the participants had at least one **indeterminate result**. Information on **false positive evaluations** is retrieved from van 't Westeinde et al.⁷¹, while the **incidental findings** estimate originates from our exploratory analysis in Section 3.2.10, but these did not have an impact on the (cost-)effectiveness outcome as stated before. Among participants with lung cancer, some represent **overdiagnosis** and some represent lung cancer with a mortality benefit from the **stage shift**. In our base case, an overdiagnosis estimate of 23.87% was applied to the screen-detected lung cancer cases. The lives saved through the stage shift in lung cancer patients is one of the effectiveness outcomes from our model.

Figure 37 – 1000-person figure of the KCE base case



Abbreviations: LDCT = low dose CT scan; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; NNS = number needed to screen. Examples of invasive tests include a biopsy or a bronchoscopy. The information used to create mutually exclusive groups after three screening rounds is published in Horeweg et al.²³⁴ Information about the number of surgeries for false positives is derived from van 't Westeinde et al.⁷¹ Note: the 1000-person figure is also available for other scenarios of overdiagnosis (see further).



Of 30 lung cancer diagnoses, four were **interval cancers** which means they were diagnosed between two screening rounds. In other words, LDCT screening may not detect all lung cancers at an early stage.

There is additional pertinent information, which is not represented in the 1000-person graph for the sake of clarity. These are nevertheless of importance when informing health providers, potential participants, and the general public regarding benefits and harms of screening:

- **Radiation risk** is not presented in the graph as these estimates are not modelled for our scenario. Considering a screening scenario with annual LDCT screening between 50 and 75 years (a scenario with 25 screens instead of 3 screens), the estimated radiation-related lifetime risk to develop cancer is estimated below 2.5 per 1000 for women and about 1 per 1000 for men.¹⁰¹
- Work-up of false positive results would result in a minor **complication** in 2.5 out of 1000 participants and a major complication in 0.4 out of 1000 participants.⁷¹
- The **incidental findings** are based on our exploratory analysis (see Section 3.2.10). Therefore, the potential health gains or losses could not be modelled.

As a **validation** (see Section 6.1.9), we compared the life years gained through stage shift in our base case with the all-cause mortality data from the NELSON trial (using the Kaplan-Meier survival curve), and versus all-cause mortality data from the meta-analysis. The difference in the number of modeled life years gained does not deviate significantly between the stage shift method in our model and the impact on all-cause mortality from the meta-analysis:

ⁱⁱ The number needed to screen (NNS) is calculated as the reciprocal of the absolute risk reduction.

With an overdiagnosis of 23.87%, we have a deviation of -0.56 life years gained per 100 participants.

With an overdiagnosis of 8.87%, we have a deviation of +0.60 life years gained per 100 participants.

Furthermore, the **anticipated absolute effects** and the **number needed to screen** (NNS)ⁱⁱ obtained from our health economic evaluation are in line with the results from the Cochrane review, which pooled mortality outcomes from 8 lung cancer screening trials. For all-cause mortality with a follow-up of 6 years to 10 years from randomisation, Bonney et al. reported a risk difference of 4 fewer per 1000 people screened (CI 1 to 8 fewer per 1000).⁵¹

Our base case with an overdiagnosis estimate of 23.87% results in an absolute risk difference of 3.3 fewer per 1000 people screened, with a follow-up of 10 years from the first screen. A scenario analysis with an overdiagnosis estimate of 8.87% results in an absolute risk difference of 4.5 fewer per 1000 people screened (see Figure 38). Of note, the meta-analysis of lung cancer-related mortality (which is not an outcome in our model) showed a relative risk reduction of 21% and an absolute risk reduction of 4 lung cancer deaths per 1000 people screened (CI 3 to 6 fewer per 1000).⁵¹

Overall, we find our model's calculation of life years gained through stage shift to be plausible.

$$\text{In our base case this results in a NNS} = \frac{1}{3.3 \text{ per 1000 people screened}} = 303$$

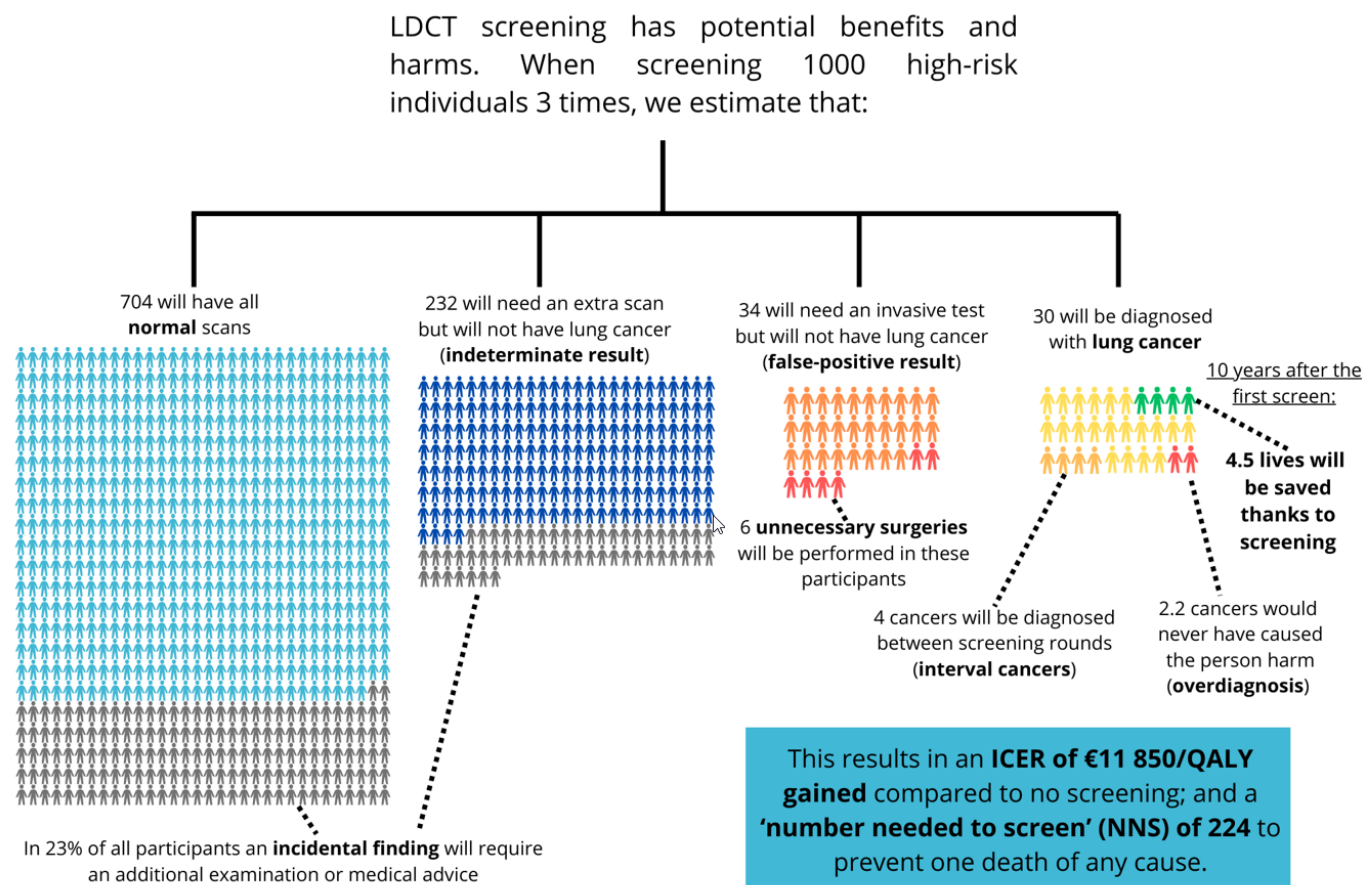


8.3.2.2. Sensitivity analysis and key cost drivers

Scenario analyses indicated that multiple variables have a substantial impact on the ICER, as shown in the tornado graph (Figure 40).

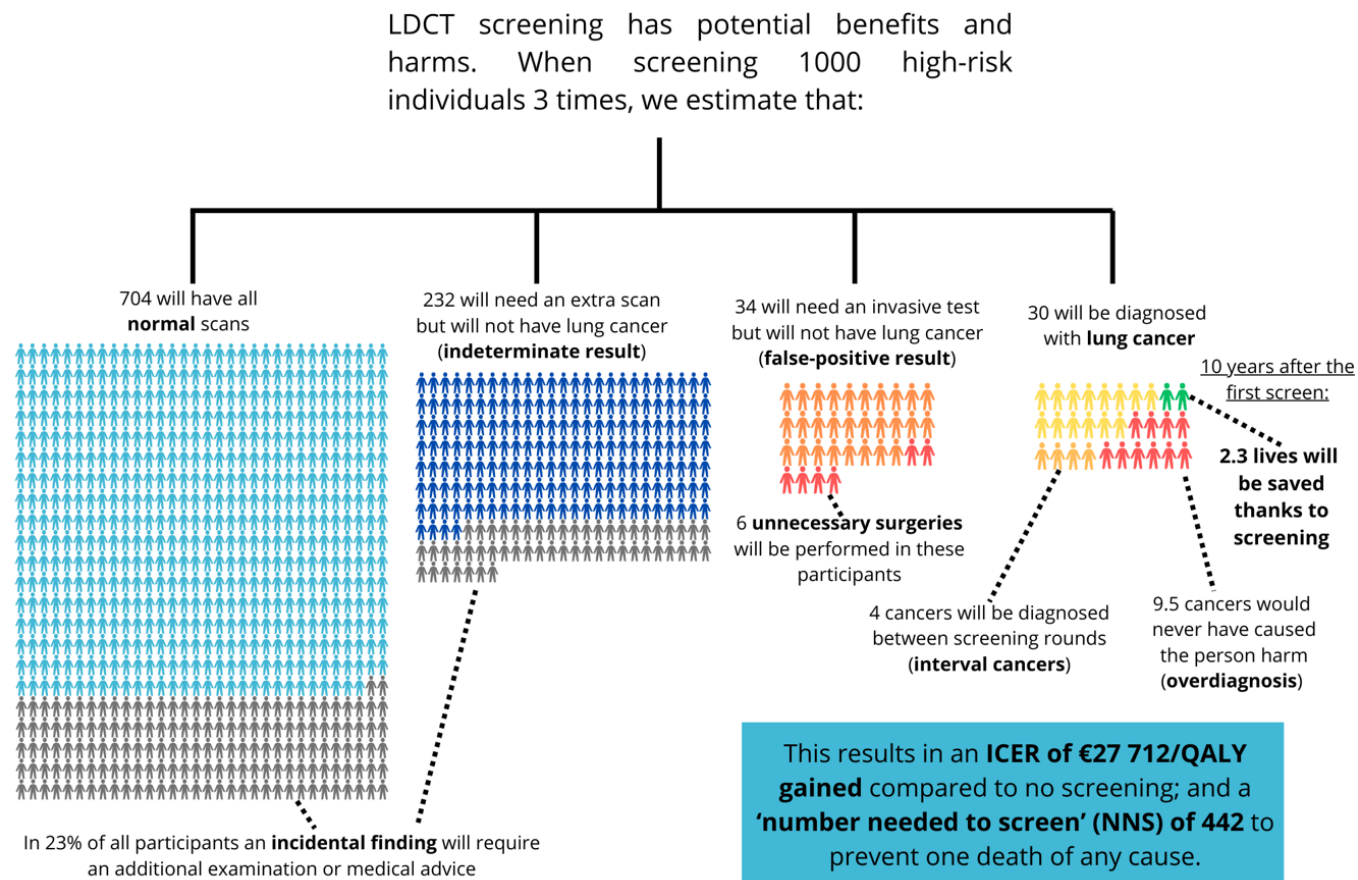
First and foremost, in line with the economic literature, the rate of **overdiagnosis** greatly influences the ICER of lung cancer screening. Various scenarios involving different overdiagnosis estimates and their effects on mortality benefits were computed, which is crucial given the uncertainties regarding overdiagnosis estimates:

- With an overdiagnosis estimate of **8.87%**, 2.2 cancers would be overdiagnosed and 4.5 lives would be saved thanks to screening 10 years after the first screening round. This results in a NNS of 224 and an ICER of €11 850/QALY gained (Figure 38).
- Vice versa, with an overdiagnosis estimate of **38%**, 9.5 cancers would be overdiagnosed and 2.3 lives would be saved thanks to screening 10 years after the first screening round. This results in a NNS of 442 and an increase in the ICER to €27 712/QALY gained (Figure 39).

**Figure 38 – 1000-person tool of the scenario with 8.9% overdiagnosis**

Abbreviations: LDCT = low dose CT scan; ICER = incremental cost-effectiveness ratio; QALY = Quality-Adjusted Life-Year; NNS = number needed to screen. Examples of invasive tests include a biopsy or a bronchoscopy. The information used to create mutually exclusive groups after three screening rounds is published in Horeweg et al.²³⁴ Information about the number of surgeries for false positives is derived from van 't Westeinde et al.⁷¹ Note: the 1000-person figure is also available for other scenarios of overdiagnosis.

Figure 39 – 1000-person tool of the scenario with 38% overdiagnosis



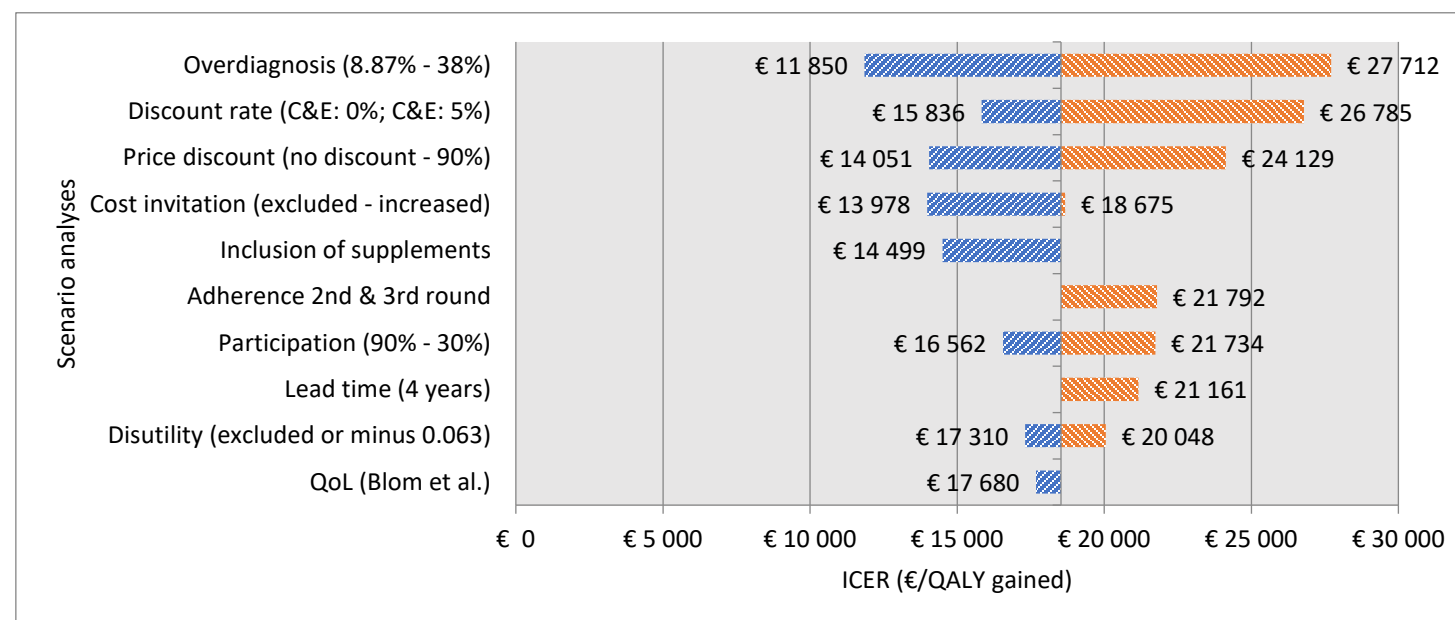
Abbreviations: LDCT = low dose CT scan; ICER = incremental cost-effectiveness ratio; QALY = Quality-Adjusted Life-Year; NNS = number needed to screen. Examples of invasive tests include a biopsy or a bronchoscopy. The information used to create mutually exclusive groups after three screening rounds is published in Horeweg et al.²³⁴ Information about the number of surgeries for false positives is derived from van 't Westeinde et al.⁷¹ Note: the 1000-person figure is also available for other scenarios of overdiagnosis.



Second, the **price discounts** for systemic therapy are identified to have a strong impact on the ICER (Box 4). The greater the discounts obtained by the government, the less cost-effective lung cancer screening is proven to be. This can be explained by an increase in incremental costs resulting from less cost savings from the stage shift as higher stage treatments become virtually cheaper.

We also identified a set of variables which appeared to have a smaller impact on the ICERs. In comparison with the above mentioned variables, increasing the participation rate, decreasing the disutilities related to false positive and indeterminate results, and using the stage utilities of Blom et al.²⁰⁸ had a relatively smaller but positive impact on the ICERs. The combination of changes in various variables together (overdiagnosis, participation, price discount) could, depending on the direction of these changes, amplify or dilute their collective influence on the ICER.

Figure 40 – Tornado graph (lifelong time horizon)



C: costs; E: effects; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; QoL: quality of life.



8.3.3. Strengths and limitations

8.3.3.1. Belgian data

The data from the Belgian cancer registry linked with the reimbursement data of the IMA – AIM database used in this report (see Section 5.2) are subject to strengths and limitations:

- The BCR data include nearly all cancer cases in Belgium and reflect recent and **real-world costs of lung cancer care** related to diagnosis, surgery, radiotherapy, immuno- and targeted therapies, and palliative care. We have nearly complete information on the stage of the disease at time of diagnosis, as well as on histological subtype. Linkage with the National Number allows to update for the **vital status** of each patient.
- These recent data allowed us to take into account the cost of **immuno- and targeted therapies**, which have substantially increased the cost of treating advanced lung cancer since 2017 when several immunotherapies were reimbursed. In 2022, approximately 80% of the expenses for systemic therapy were attributed to immunotherapy, with targeted therapy accounting for around 15% (Figure 16). The drug expenditures are gross expenditures not taking into account the impact of confidential discounts and taxes (see Box 4).
- A limitation is that BCR does not have information related to subsequent **disease progression/recurrence**, but since all costs related to radio- and chemotherapy, as well as immuno- and targeted therapies were included, this is unlikely to have a large impact.
- Due to the administrative data's lack of specificity, costs related to **complications** occurring after discharge following surgery or systemic therapy administration, as well as complications related to radiotherapy, could not be included.
- Additionally, there is a potential for stage classification changes over time due to the **adoption of the TNM-8 classification** in the BCR data since 2017. However, since the data are presented by stage (I-IV) rather than by substages, the transition from the seventh to the eighth edition had a limited impact on our sample.
- As stated before, **data on smoking** (history) from the Belgian population is not available at the individual level in any database. Patients could

thus not be selected for this characteristic. Individuals with a lung cancer incidence date before the start of our interval were also excluded, as we argued these would be followed-up instead of being eligible for screening. Furthermore, individuals with a non-lung cancer incidence before the start of our interval were also excluded, to best reflect lung-cancer related costs in our sample, as it is not possible to differentiate for instance between radiotherapy for lung cancer and radiotherapy for another cancer with an incidence date near to the lung cancer incidence. We acknowledge that in the real-world setting, individuals who were treated for e.g., an early-stage endometrial cancer would be eligible for lung cancer screening.

- Since cost analyses are not the main mission of the BCR, IMA – AIM data are not exhaustively transmitted to the BCR. Health care interventions that can be linked to the management of cancer are routinely transmitted, but some sections of the Belgian RIZIV – INAMI nomenclature are not transmitted, such as physiotherapy. The **list of exclusions** can be found in Appendix 10.1. Overall, the impact should be limited as the costs calculated in the present report pertain to cancer management. The same principle applies to some pharmaceuticals, see Appendix 10.2 for the ATC unavailable in BCR – IMA – AIM data. Again, we can be confident that most relevant costs are included in our calculations.
- Other limitations are linked to **specificities of the Belgian health care system**. First, the system of maximum billing puts a ceiling on the total amount of co-payments at the level of a household during a calendar year, where the ceiling is a function of the household income. When the ceiling is exceeded, the national health insurance fully reimburses health care costs (except for supplements). While in the IMA data the total amount of waived co-payments and increased health insurance reimbursements are equal at the household level, this is not necessarily the case at the individual patient level, because sickness funds can choose how they register the reimbursements (for example, an equal amount in the record of each household member). In our analysis, no correction was applied for this (limited) bias. Furthermore, there was no correction for the Global Payment System, applicable since 2019 (not for pharmaceuticals). When the Global Payment System applies,



individual fee-for-services are put to zero as health care is covered by a global lump sum. There could thus be an underestimation of costs. We estimate that the bias was limited: e.g., only 0.26% of the records were concerned in the diagnostic costs.

In the end, although there are some limitations to the available BCR and IMA – AIM data, the possibility to perform data analyses on this real-world data for diagnostic, radiotherapy, surgery, systemic therapy and palliative costs stratified per stage of lung cancer is a major strength of this Belgian economic evaluation.

8.3.3.2. *Combining strengths (and addressing shortcomings) of the previously published economic literature*

In the cost-effectiveness analysis in this report, both the strengths and shortcomings identified in other published models were addressed as much as possible:

- In contrast to a considerable number of identified studies assuming a **participation rate** of 100%, our model took the participation rates as observed in the NELSON trial into account. Additional scenario analyses were performed with higher and lower participation rates to estimate the impact of the participation rate on the cost-effectiveness of LCS.
- In addition, while assumed to be 100% by the majority of identified studies, our model does account for the **adherence rate** in subsequent screening rounds as observed in the NELSON trial. As one could argue the adherence outside the research setting might be lower, an additional scenario analysis was conducted assuming considerably lower participation rates in the second and third screening rounds.
- While being one of the major challenges related to LCS, the majority of the studies identified in the economic review did not disclose the procedure used to identify and invite screen-eligible candidates. Our model described a potential **invitation procedure** in close cooperation with experts in the field. Costs were assigned to this procedure using Belgian data obtained from existing screening programmes.
- It was decided to base our model on the **NELSON trial**, including its screening eligibility criteria and screening intervals. While this choice does not enable us to model the impact of changes in eligibility criteria or screening intervals, the model does provide an objective representation of the evidence as observed in the NELSON trial. The direction of the impact of broadening or narrowing the eligibility criteria can be argued based on the trends in the published literature (as well as intuition). For example, lowering the start age or increasing the stop age of screening is expected to worsen the cost-effectiveness of LCS due to the relation between LC incidence and age in case of the former and increased overdiagnosis in the case of the latter. Likewise, it is expected that moving from the mixed annual and biennial screening in the NELSON trial to annual screening leads to less favourable ICERs as we expect incremental effects to increase proportionally less than the incremental costs. However, to gain more certainty on the magnitude of this impact, or the impact of e.g., only increasing the screening interval for a specific high-risk subgroup, additional evidence from future and/or ongoing trials is needed (e.g., 4-IN THE LUNG RUN).
- While the published literature generally did not explicitly disclose how **false negative results** were handled, false negatives in our model are assumed to be detected in an upcoming screening round or to be incorporated in the interval cancers.
- Although one of the major potential harms related to LCS, only a handful of the identified studies disclosed taking into account **false positives** in their analyses. These studies either assigned an additional cost to false positive results or a disutility, but only three did both. In our model, both a cost and temporary disutility are assigned to false positives based on NELSON trial data. Likewise, this analysis also assigns a cost and temporary disutility to indeterminate results, which was only done by two of the identified economic evaluations.
- In addition to false positives, **overdiagnosis** is considered to be a substantial harm of LCS. While half of the economic evaluations did not account for overdiagnosis, leading to overly optimistic ICERs, our model did consider overdiagnosis by separating the overdiagnosed cases and assigning a cost to these cases. In other words, this means that



overdiagnosed LCs do not lead to beneficial health effects but induce additional costs due to LCS.

- Survival data obtained from observational data comparing survival data from screen-detected cancers with non-screen detected cancers may be overoptimistic due to **lead-time bias and length-time bias**. Data from RCTs overcome these biases by taking the date of randomisation as starting point instead of the date of diagnosis and by including all patients diagnosed with lung cancer, both screen-detected and interval cancers. Length bias is implicitly taken into account as fast growing cancers are included in the interval cancers. For lead-time bias the impact of earlier starting treatment is reflected only through applying a longer time window when applying the discount rate for costs in the comparator group without LCS.

Nevertheless, some limitations have to be taken into account when interpreting the results from our model:

- The impact of **incidental findings** is not included in the model due to a lack of evidence on the direction and magnitude of the impact. Further research needs to be done in order to quantify the health gains or losses of incidental findings associated with LDCT screening.
- Furthermore, the model suffers from two limitations related to **QoL**. First, the stage utilities of NSCLC were assumed to be identical to the stage utilities of SCLC. We argue the impact of this assumption is minor as the proportion of SCLC in the sample is minimal (1.8%-7.8% over the three screening rounds). Important to note is that SCLC-specific costs and survival were used from BCR - IMA – AIM data, only the stage utilities were assumed to be equal to those of NSCLC. Second, overdiagnosis and lead-time bias are not associated with a decrease in QoL in our model due to a lack of evidence on the magnitude and duration of this QoL loss. Our base case therefore assumed no changes in QoL due to overdiagnosis and lead-time bias.
- A limitation of opting for the trial-based modeling approach, is the limited **flexibility of our model** compared to disease modelling. This means that the model is not able to evaluate multiple screening eligibility criteria and/or screening intervals. However, based on the published

literature and data trends it is possible to formulate arguments on the direction of the impact (e.g., annual vs biennial screening). A potential shortcoming of disease modelling, a methodology opted for by a selection of studies identified in the economic literature review, is the lack of reflecting the identified evidence. The model of UK NSC for example substantially overestimated the proportion of stage IV lung cancers and underestimated the proportion of mainly stage I and II lung cancers compared to UK national statistics.¹¹⁶ We therefore chose to provide an objective representation of the evidence as observed in the NELSON trial to avoid these problems.

- It is possible that some LCS-specific costs were over- or underestimated in the model (e.g., cost of invitation, one-off investment cost for IT system CvKO, quality control). For example, the costs of hosting, updating, providing support,... for the website used to check the eligibility of potential participants in the hypothetical invitation scenario were not included. However, relative to the total cost of screening (approx. €50 million), these costs (estimated at €25 000 to €50 000) can be considered negligible.
- It could be argued that the **participation rate** of an RCT might be lower than the one of an evidence-based screening programme. To estimate the impact of participation rate on the cost-effectiveness of screening we incorporated scenario analyses reflecting higher and lower participation rates respectively. In addition, as screening adherence of the NELSON trial might be optimistic, an additional scenario analysis was conducted assuming considerably lower participation rates in the second and third screening rounds to estimate the impact of lower screening adherence on the cost-effectiveness.
- While our health economic model integrated RCT evidence supplemented with recent Belgian real-world data, it doesn't necessarily represent an actual LDCT screening program. As NELSON started nearly two decades ago, the use of **more recent screening protocols** may have an impact on the balance of benefits and harms of LDCT screening, but many more assumptions will be made when trying to model these. At the same time, the screening-eligible population may



also have changed, for instance regarding cardiovascular disease and competing risks of mortality.

Finally, this economic evaluation was conducted using the latest available data on costs and survival specific to stage and histology, which we consider a major strengths. Nevertheless, it is important to note that **changes in the treatment of lung cancer patients** (e.g., immunotherapy in early-stage NSCLC²⁷⁶) may have an impact on the incremental costs and effects associated with the stage shift. A smaller gain in life years or cost savings from a stage shift to earlier lung cancer detection will thus result in a higher ICER (and vice versa).

8.4. Ethical considerations

8.4.1. *Is it ethical to implement a national cancer screening programme based on individual behaviour?*

Implementing a national cancer screening program based on individual behavior raises significant ethical considerations. While the aim is to target high-risk populations, this approach may inadvertently contribute to health disparities and stigmatization. Recent research, such as the work by Carter-Harris et al,²⁶³ underscores the ethical challenges associated with linking cancer screening programs to individual behaviors, particularly when addressing cancers related to lifestyle factors such as smoking. The potential for blaming individuals for their health outcomes and the risk of reinforcing societal biases should be carefully considered. Ethical guidelines, as emphasized by Juth et al,²⁵⁰ stress the importance of ensuring equity, autonomy, and informed consent in population-based screening programs. Striking a balance between the public health benefits of early detection and the ethical implications of singling out individuals based on behavior is crucial for the successful and morally sound implementation of national cancer screening initiatives.

Recent research, including the work of Burzic et al.²⁶² highlights the need to carefully manage this tension, taking into account the ethical implications of balancing the wider public health benefits of early detection against the potential risks and burdens for individuals. Balancing the ethical

considerations of individual autonomy and informed decision-making with the overarching goals of public health is essential to the development of effective and morally sound health policies for lung cancer screening. This ethical tension highlights the complexity of formulating policies that both address population-level health outcomes and respect the rights and preferences of individuals.

Finally, screening can give rise to concerns about privacy and confidentiality, since results can be interpreted as revealing personal health behaviors. This stigmatizing dimension of lung cancer screening underscores the importance of adopting a holistic approach that incorporates psychosocial and ethical considerations in the implementation of screening programs, in order to minimize the negative impact on the mental health and well-being of the individuals concerned.²⁶³

8.4.2. *How to reach the 'hard-to-reach'?*

The success and effectiveness of lung cancer screening programmes depend on the level of participation²⁶². Indeed, if only a minority would participate, there will be no mortality reduction on the population level. As stated by van Hal et al,²⁵³ '*compared to the target groups for screening in the long-running cancer screening programs of breast, cervical and colorectal cancer, there are several additional obstacles regarding defining, locating and recruiting of the target group for lung cancer screening*'. Emotional barriers (regret, guilt and feelings of entrapment, (anxiety, fear and the need to avoid lung cancer related information) are the main reasons justifying barriers to recruiting the target population.^{254, 261, 262}

Furthermore, recent research amongst others conducted by Burzic et al.²⁶² and van Hal et al.²⁵³ highlights the ethical complexities associated with disparities in screening uptake and the potential amplification of existing health inequalities. These studies emphasise the need to take account of the social determinants of health and to adapt screening strategies to the specific needs of marginalised or underserved communities. Factors such as distrust of health systems, cultural diversity and limited health knowledge in 'hard-to-reach' populations pose ethical challenges that require culturally sensitive approaches and community engagement strategies. Reaching the 'hard-to-reach' populations is a pivotal challenge in the context of lung



cancer screening, and recent research has delved into effective strategies to overcome this barrier. Studies, such as the work by Carter-Harris et al,²⁶⁴ emphasize the importance of targeted outreach and culturally tailored communication to engage populations that may face socio-economic, geographic, or cultural obstacles to screening participation. Implementing community-based interventions and leveraging technology can enhance accessibility for individuals in remote or underserved areas. Nonetheless, as highlighted by Burzic et al,²⁶² individuals in challenging-to-reach communities, especially those with lower socio-economic status, may be excluded from this technology due to the typical demographic characteristics of smartphone users: being younger, better educated, and having higher incomes.

8.5. Considered out of scope, nevertheless key elements in a lung cancer screening programme

An in-depth review of the evidence for effectiveness and cost-effectiveness of a screening programme is an essential step before deciding on implementation. When effectiveness and cost-effectiveness are proven, other factors such as impact on the health system, the financial impact/affordability also need to be taken into account.⁹ Additionally, participant selection, integration of smoking cessation interventions, and screening intervals (e.g., annual vs biennial) can significantly affect the cost-effectiveness of a lung cancer screening programme. While these factors were not explicitly addressed in our systematic review or included in the cost-effectiveness analysis, these are essential factors when considering LCS implementation.

8.5.1. Budget impact

After an analysis of the safety, efficacy and cost-effectiveness, a budget impact analysis could be performed to assess the financial impact of integrating the screening programme into the healthcare system. However, within the time restrictions of the project, it was decided to focus in first instance on the clinical criteria (safety and efficacy) and the acceptability (cost-effectiveness) of the programme. From an economic point of view, when trying to provide advice on the efficient use of limited resources,

priority should be given to an intervention's cost-effectiveness (i.e., the expected incremental costs of the intervention in relation to the expected incremental benefits) rather than its budget impact. If decision makers would decide to support the introduction of a LCS programme, a budget impact analysis can be further developed and supported by the info available in this report.

8.5.2. Impact on the health system

Implementing a screening programme requires resources, not only in terms of money but also in terms of workforce and technical capacity. A population-based screening programme involves a series of activities, such as identification of the potentially eligible population, providing accurate information about the benefits and harms, organization of the screenings, performing the LDCT scan, interpreting results, conducting follow-up tests, providing counselling and treatment, and managing patient data. Each of these activities requires a skilled workforce, among others, radiologists, radiology technicians, pulmonologists, thoracic surgeons, oncologists, nurses, and administrative staff. Therefore, when considering the implementation of a lung cancer screening programme in Belgium, it is crucial to assess the capacity of the entire workforce involved in the process, and to ensure that services have the capacity to deal with additional referrals.

Primary healthcare providers, who may play an important role in recruiting participants for lung cancer screening, can also face barriers such as inadequate time to discuss the benefits and harms of lung cancer screening, limited knowledge about screening, concerns about health system burden and costs, and lack of clear management pathways for incidental findings.^{20.}

²⁷⁷ The estimated prevalence of incidental findings in lung cancer screening, as discussed in Section 3.2.10, is expected to necessitate additional downstream management for a substantial proportion of participants, which underlines the importance of screening protocols that include the reporting and management of these incidental findings.

Another major requirement is having sufficient capacity to conduct CT scans, and concerns have been raised about the availability of CT scanners in Belgium for implementing a LCS programme.²⁷⁸ CT-scan capacity in Belgium is slightly below the OECD average, while the number of exams



performed is higher compared to the OECD average. It's important to consider the potential impact on waiting times for CT scans before making a final decision regarding the implementation of lung cancer screening in the various regions of Belgium.²⁷⁹ Of note, the Swiss Cancer Screening Committee recommended biennial screening, citing capacity concerns with respect to annual screening.²⁸⁰

8.5.3. *Invitation of participants, recruitment, participation*

Response to recruitment to screening programmes in the trial setting ranged from 1% to 5% of people approached with invitations and letters.⁵¹ In the USA, there has been concern about the low uptake of lung cancer screening after it was approved by the USPSTF, with fewer than 4% of eligible participants have had screening based on 2016 national Lung Cancer Screening Registry data.^{20, 281}

In our model, we used the response and participation rates as experienced in the NELSON trial, partially performed in Belgium, acknowledging that the population who participates and engages in a trial may not be reflective of the general population. When people receive information regarding the known benefits and harms of lung cancer screening, uptake may be higher compared to participation in a randomised trial. In the UK, a 53% participation rate was achieved with a targeted approach with invitations via their primary care practitioner offering prescheduled appointments. Information about lung cancer screening was provided during a visit at the general practice.²⁸² If a lung cancer screening programme would be implemented in the Belgian regions, it should be similarly tested and piloted how a sufficiently high participation rate can be achieved in a cost-effective way, considering different participant recruitment strategies. In Flanders, first initiatives have been taken in the region of Antwerp.²⁸³

8.5.4. *Integration of smoking cessation*

Combining LDCT with effective smoking cessation programmes optimises the mortality benefit of lung cancer screening programmes by reducing the risk of lung cancer and other tobacco-related diseases including COPD, cardiovascular disease, and other cancers.²⁰ The scope of this report was specifically aimed at the cost-effectiveness of LCS alone, and our model did not take into account a specific smoking cessation intervention in combination with LCS. Smoking cessation interventions are already available to the population and are known to be cost saving, which would confound the cost-effectiveness of LCS. The economic evaluations focusing on adding a smoking cessation intervention to LCS, previously identified in the economic literature review, demonstrate a favourable impact on the cost-effectiveness of adding a specific smoking cessation intervention to LCS. In case LCS would be implemented, it is essential to integrate existing smoking cessation interventions in close collaboration with all relevant stakeholders. Ongoing pilot and implementation studies such as the HANSE study in Germany or the 4-IN THE LUNG RUN^{jj} aim to provide additional evidence of incorporating smoking cessation into LCS.^{65, 231}

8.5.5. *Screening intervals*

Extending the interval between LDCT scans for screening participants at lower risk of lung cancer could substantially reduce the number of scans performed each year, thereby reducing screening programme costs and radiation dose to the individual. Based on the currently available evidence, there remains uncertainty about the effect of biennial compared to annual LDCT screening on mortality. The included LCS trials mostly used annual screening intervals (see Table 6). Within the MILD trial, biennial as compared to annual LDCT screening resulted in similar mortality benefits, although concerns were raised regarding the methodological quality of the trial.⁵⁰ The NELSON trial, which was used as input for our economic model,

^{jj} 4-IN THE LUNG RUN: Individually tailored INvitations, screening INtervals, and INtegrated co-morbidity reducing strategies in lung cancer screening is a multicenter implementation trial underway in five European countries and is aiming to answer questions about personalized strategies in recruitment,

screening intervals (biennial versus annual in those with a negative baseline LDCT), smoking cessation and other add-on health interventions for co-morbidity such as CAD and COPD. The planned study end date is December 2024.



used incremental intervals of 1 year, then 2 years, and added a fourth screening round with a 2.5 year interval.¹⁰ The increased number of (later-stage) interval cancers at an interval of 2.5 years, suggested that the duration of this screening interval leads to a decreased effectiveness.²²⁹

The uncertainties in the current evidence are reflected in the formulation of the European Technical Standard of the European Respiratory Society,⁹⁸ stating the following:

- “Annual LDCT is the preferred interval if capacity and total economic and health service impact allow.
- Biennial intervals may be applied for lower risk groups using LDCT findings or multivariable risk prediction models to select participants.
- Screening intervals should not exceed 2 years.”

In this report, cost-effectiveness was calculated according to the characteristics of the NELSON trial (both by population selection, as well as the screening intervals applied). We agree with the above third statement given the large number of interval cancers after two years. Related to the first statement, we did not estimate the cost-effectiveness of annual screening. However, systematically applying an annual screening interval will most likely reduce the cost-effectiveness. The number of interval cancers identified in the second year of the interval in the NELSON trial is proportionally smaller in relation to the extra costs related to yearly screening. In addition, there is also the organisational and budgetary impact if annual screening were to be applied to all participants.

Based on future evidence, a more accurate calculation can be made. It is important to note that there is active research underway on personalized screening intervals, with ongoing trials such as the 4-IN-THE-LUNG-RUN trial and the SUMMIT trial specifically comparing biennial and annual screening intervals for participants with negative baseline LDCT results.²³¹

8.5.6. *Quality and performance management*

One of the Dobrow principles for screening programmes (see Table 1) states that a screening programme should explicitly be linked to programme planning, monitoring, evaluating and reporting activities to ensure ongoing quality control and achievement of performance targets. This requires a performant IT system and continuous data collection. Monitoring and evaluation of screening programmes is necessary to ensure that the screening programmes are as effective as expected and to ensure public trust in the programme.^{9, 284}

Within a quality assurance system, screening standards are developed to assess and drive screening performance. As for other screening programmes, screening standards could include outcome measures such as cancer detection rates, false positive rates, harms related to invasive procedures, turnover times etc.^{282, 284} Furthermore, auditing the reporting and management of incidental findings and training programmes for radiologists can be included in quality assurance for lung cancer screening.²⁸²

The regional agencies in Belgium responsible for the organisation of screening programmes have experience in such a performance management, in collaboration with the BCR.^{272, 285}



9. OVERALL CONCLUSION

Screening for lung cancer with LDCT in high-risk individuals can reduce lung cancer-specific mortality and overall mortality among participants, but the potential harms must be considered, especially those related to overdiagnosis and false positive results. LDCT screening also results in a significant number of incidental findings, and it remains unclear whether they benefit or harm participants. Additionally, each participant is subjected to radiation exposure.

LDCT screening can be cost-effective if the policymaker's willingness to pay ranges between €20 000 and €30 000 per QALY gained. However, despite the potential cost-effectiveness of LDCT screening, the balance between clinical benefits and harms is less clear-cut and must be carefully weighed by policymakers. The impact on available budgets and capacity within the healthcare system (both technical and workforce) will also play a significant role in decision-making. Finally, if a screening program were to be implemented, every participant must be clearly informed about the benefits and harms beforehand to facilitate an informed decision. This ethical obligation must be respected, even if it leads to a decrease in participation rates.



■ APPENDICES

APPENDIX 1. SEARCH STRATEGY – WEBSITES HTA INSTITUTES

In October 2022, the websites of the INAHTA members (Table 94) were searched using the free text 'lung cancer screening'.

Table 94 – List of INAHTA member websites searched for HTA reports

Abbreviation	Institute	Country
ACE	Agency for Care Effectiveness	Singapore
AETS	Agencia de Evaluación de Tecnologías Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AGENAS	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AIHTA	Austrian Institute for Health Technology Assessment	Austria
ANS	Agência Nacional de Saúde Suplementar/ National Regulatory Agency for Private Health Insurance and Plans	Brazil
AOTMiT	Agency for Health Technology Assessment and Tariff System	Poland
AP-HP	Assistance publique- Hopitaux de Paris	France
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya	Spain
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CA-HTA	Central Administration of Health Technology Assessment	Egypt
CDE	Center for Drug Evaluation	Taiwan
CONITEC	National Committee for Technology Incorporation	Brazil



Abbreviation	Institute	Country
DEFACTUM	Social & Health Services and Labour Market	Denmark
FinCCHTA	Finnish Coordinating Center for Health Technology Assessment	Finland
G-ba	The German Health Care System and the Federal Joint Committee	Germany
GÖG	Gesundheit Österreich	Austria
HAD-Uruguay	Health Assessment Division, Ministry of Public Health	Uruguay
HAS	Haute Autorité de Santé	France
HIQA	Health Information and Quality Authority	Ireland
HIS	Healthcare Improvement Scotland	United Kingdom
HTW	Health Technology Wales	United Kingdom
IACS	Health Sciences Institute in Aragon	Spain
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IETS	Instituto de Evaluación Tecnológica en Salud	Colombia
IETSI	Institute of Health Technology Assessment and Research	Peru
IHE	Institute of Health Economics	Canada
INEAS	National Authority for Assessment and Accreditation in Healthcare	Tunisia
INESSS	Institut national d'excellence en santé et en services sociaux	Canada
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
MaHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia	Malaysia
NECA	National Evidence-based healthcare Collaboration Agency	Korea
NICE	National Institute for Health and Care Excellence	United Kingdom
NIHO	National institute for Value and Technologies in Healthcare	Slovak Republic
NIHR	National Institute for Health Research	United Kingdom



Abbreviation	Institute	Country
NIPH	Norwegian Institute of Public Health	Norway
OH	Ontario Health	Canada
OSTEBA	Basque Office for Health Technology Assessment	Spain
RER	Regione Emilia-Romagna	Italy
SK-NRCHD	Salidat Kairbekova National Research Center for Health Development	Kazakhstan
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
SEC	Department of HTA at the State Expert Centre of the Ministry of Health	Ukraine
SFOPH	Swiss Federal Office of Public Health	Switzerland
UVT	HTA Unit in A. Gemelli University Hospital	Italy
ZIN	Zorginstituut Nederland	The Netherlands
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands

Twenty-eight HTA reports were identified. Six reports included an overview of existing economic evaluations or performed a de novo economic evaluations. Table 95 and Table 96 provide an overview of the selected and excluded reports (incl. the reason for exclusion).

Table 95 – List of included HTA reports

References	
Selected HTA reports	
Austrian Institute for Health Technology Assessment (AIHTA). Lung cancer screening in risk groups: A review-update of the economic evidence. Vienna: AIHTA. 2020	Update-review economic evaluations
Institute of Health Economics (IHE). Low dose computed tomography for the screening of lung cancer in adults. Edmonton AB: Institute of Health Economics. 2014.	Primary economic evaluation
Health Technology Assessment Section at Ministry of Health of Malaysia (MaHTAS). Low dose computed tomography for lung cancer screening. No year of publication mentioned.	Review economic evaluations
Swedish Council on Technology Assessment in Health Care (SBU). Computed tomography in screening for lung cancer. December 2002.	Review economic evaluations



UK National Screening Committee (NSC). Interim report on the cost-effectiveness of low dose computed tomography (LDCT) screening for lung cancer in high risk individuals. March 2022.	Primary economic evaluation
UK National Screening Committee (NSC). Targeted screening for lung cancer in individuals at increased risk. September 2022.	Review economic evaluations

Table 96 – List of excluded HTA reports

References	Reason for exclusion
Agency for Care Effectiveness (ACE). When not to order chest X-ray. ACE Clinical Guidance (ACG), Ministry of Health, Singapore. 2021. Available from: go.gov.sg/acg-when-not-to-order-chest-x-ray	Clinical, imaging
Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA). Cribado selectivo del cáncer de pulmón con tomografía computarizada de tórax. 2007.	Spanish
Agency for Healthcare Research and Quality (AHRQ). Lung Cancer Screening: An Update for the U.S. Preventive Services Task Force. Systematic Evidence Review Number 31. May 2004.	Clinical
Austrian Institute for Health Technology Assessment (AIHTA). Lung cancer screening in risk groups: Systematic Review of Harms and Benefits. Vienna: AIHTA. 2020	Clinical
Galician Agency for Health Technology Assessment (AVALIA-T). María del Carmen Sánchez González, Paula Cantero Muños y Gerardo Atienza Merino. Low-dose computed tomography screening for lung cancer. 2016.	Spanish
Canadian Agency for Drugs and Technologies in Health (CADTH). Lung-RADS Versus Pan-Canadian Early Detection of Lung Cancer Study Screening for Patients at High Risk of Lung Cancer. CADTH Health Technology Review. December 2021.	Diagnostics
Canadian Agency for Drugs and Technologies in Health (CADTH). Artificial Intelligence for Classification of Lung Nodules: Clinical Utility, Diagnostic Accuracy, Cost-Effectiveness, and Guidelines. Ottawa: CADTH; 2019 Nov. (CADTH rapid response report: summary of abstracts).	Intervention
Canadian Agency for Drugs and Technologies in Health (CADTH). Artificial intelligence for classification of lung nodules: clinical utility, diagnostic accuracy, cost-effectiveness and guidelines. (CADTH rapid response report: summary with critical appraisal). Ottawa: CADTH; 2020 Jan.	Intervention
Canadian Agency for Drugs and Technologies in Health (CADTH). Lung Cancer Screening: Clinical Utility and Guidelines. Ottawa: CADTH; 2020 Sept. (CADTH rapid response report: reference list).	Clinical, guidelines
Canadian Agency for Drugs and Technologies in Health (CADTH). Emerging Multi-Cancer Early Detection Technologies. CADTH Horizon Scan. April 2022.	Intervention
Haute Autorité de Santé (HAS). Cancer du poumon: évaluation de la pertinence d'un dépistage des populations fortement exposées au tabac en France. Note de cadrage. Septembre 2014.	Clinical
Haute Autorité de Santé (HAS). Pertinence du dépistage du cancer broncho-pulmonaire en France. Point de situation sur les données disponibles. Analyse critique des études contrôlées randomisées. Rapport d'orientation. Janvier 2016.	Clinical



Haute Autorité de Santé (HAS). Dépistage du cancer bronchopulmonaire par scanner thoracique faible dose sans injection: Actualisation de l'avis de 2016. Rapport d'orientation. Décembre 2021.	Clinical
Health Improvement Scotland (HIS). Calvert J. Evidence synthesis: Targeted screening for early lung cancer in adults at high risk. Rapid Response. January 2021.	Clinical
Institut national d'excellence en santé et en services sociaux (INESSS). Indications de la tomographie par émission de positrons en oncologie - Cancer du poumon. Janvier 2017.	Clinical
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Lung cancer screening with low-dose computed tomography. October 2020.	Clinical
Health Technology Assessment Section at Ministry of Health of Malaysia (MaHTAS). Lung Cancer Risk Prediction Model for National Health Risk Assessment Module. 2015.	Intervention
Health Technology Assessment Section at Ministry of Health of Malaysia (MaHTAS). Early detection of common cancers and referral pathways: module for health care providers. 2017.	Clinical
Health Technology Assessment Section at Ministry of Health of Malaysia (MaHTAS). National strategic plan for cancer control programme (2016-2020). 2017.	Clinical
Health Technology Assessment Section at Ministry of Health of Malaysia (MaHTAS). National strategic plan for cancer control programme (2021-2025). 2021.	Clinical
National Institute for Health and Care Excellence (NICE). Lung cancer: diagnosis and management. NICE guideline 122. March 2019.	Intervention
Basque Office for Health Technology Assessment (OSTEBA). Screening del cancer de pulmon. Aspectos novedosos. September 2012.	Spanish
National Health Service (NHS). Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography. Standard Protocol prepared for the Targeted Lung Health Checks Programme. January 2019.	Clinical
UK National Screening Committee (NSC). Screening for lung cancer. March 2007.	Clinical



APPENDIX 2. SEARCH STRATEGY – MEDICAL LITERATURE

Table 97 – Search strategy Cochrane Database of Systematic Reviews

Date	February 23, 2023	
Database	Cochrane Database of Systematic Reviews	
Search strategy		
1	MeSH descriptor: [Lung Neoplasms] explode all trees	10 232
2	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	5 671
3	MeSH descriptor: [Small Cell Lung Carcinoma] explode all trees	532
4	"Cancer of Lung*" or "Cancer of the Lung*" or "lung cancer*" or "lung malignan*" or NSCLC or "Pulmonary Cancer*" or "Pulmonary tumo*"	24 180
5	#1 or #2 or #3 or #4	25 930
6	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees	7 048
7	MeSH descriptor: [Mass Screening] explode all trees	5 271
8	MeSH descriptor: [Early Diagnosis] explode all trees	2 656
9	"CT Scan*" or "Computed Tomography" or "CAT Scan" or "Computerized Tomography" or "CT X Ray*" or "LDCT" or "screen*":kw	21 664
10	#6 or #7 or #8 or #9	31 003
11	#5 and #10	1 852
12	#11 with Cochrane Library publication date Between Jan 2020 and Mar 2023, in Cochrane Reviews	7
Comments		

**Table 98 – Search strategy Medline**

Date	February 23, 2023	
Database	Medline	
Search strategy		
1	"Lung Neoplasms"[MeSH] OR "Carcinoma, Non-Small-Cell Lung"[MeSH] OR "Small Cell Lung Carcinoma"[MeSH] OR ("Carcinoma, Squamous Cell"[Mesh] OR "Adenocarcinoma"[MeSH]) AND ("Lung"[MeSH] OR "Lung Diseases"[MeSH])) NSCLC[tiab] OR "lung cancer"[tiab] OR "lung-cancer"[tiab] OR "lung malignan"[tiab] OR "pulmonary Cancer"[tiab] OR "Pulmonary tumo"[tiab]	206 313
2	"Mass Screening"[MeSH] OR "Early Detection of Cancer"[Mesh] OR "Early Diagnosis"[MeSH] OR "Tomography, X-Ray Computed"[Mesh] OR "low-dose computed tomography"[tiab] OR "LDCT"[tiab] OR "low-dose computed tomography"[tiab] OR "LDCT"[tiab] OR "CT scan"[tiab] OR "CAT scan"[tiab]	732 169
3	"systematic review"[ti] OR "systematic literature review"[ti] OR "systematic scoping review"[ti] OR "systematic narrative review"[ti] OR "systematic qualitative review"[ti] OR "systematic evidence review"[ti] OR "systematic quantitative review"[ti] OR "systematic meta-review"[ti] OR "systematic critical review"[ti] OR "systematic mixed studies review"[ti] OR "systematic mapping review"[ti] OR "systematic cochrane review"[ti] OR "systematic search and review"[ti] OR "systematic integrative review"[ti] OR ("Cochrane Database Syst Rev"[ta] AND "review"[pt]) OR "systematic review"[pt] OR "meta-analysis"[pt] OR "meta-analysis"[ti]	368 751
4	#1 AND #2 AND #3	283
5	#4 AND ("2020/01/01"[Date - Publication] : "3000"[Date - Publication])	103
Comments		

Table 99 – Search strategy Embase

Date	February 23, 2023	
Database	Embase	
Search strategy		
1	'lung carcinoma'/exp OR 'non small cell lung cancer'/exp OR 'small cell lung cancer'/exp	265 234
2	'nsccl':ti,ab OR 'lung cancer*':ti,ab OR 'lung-cancer*':ti,ab OR 'lung malignan*':ti,ab OR 'pulmonary cancer*':ti,ab OR 'pulmonary tumo*':ti,ab OR 'lung neoplasm*':ti,ab OR 'lung tumo*':ti,ab	329 852
3	#1 OR #2	417 932
4	'x-ray computed tomography'/exp	96 425
5	'ct scan*':ti,ab OR 'cat scan':ti,ab OR 'computed tomography':ti,ab OR 'low-dose computed tomography':ti,ab OR 'ldct':ti,ab	532 236



6	#4 OR #5	574 628
7	#3 AND #6	29 368
8	#7 AND ([systematic review]/lim OR [meta analysis]/lim)	467
9	#8 AND [2020-2023]/py	178

Comments

Table 100 – Excluded reviews and reason for exclusion

	Year	Publication	Reason for exclusion
1	2020	Dezube A, Jaklitsch M. New evidence supporting lung cancer screening with low dose CT & surgical implications. Eur J Surg Oncol. 2020;46(6):982-990	Narrative review
2	2020	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Lungenkrebscreening mittels Niedrigdosis-Computertomografie. Köln: IQWiG; 2020. https://www.iqwig.de/projekte/s19-02.html	German language. Meta-analysis identical as EUnetHTA
3	2020	Sanz C, Rodriguez T. Lung cancer screening: A systematic review. Ann Oncol. 2020; 31 S964	Abstract presented only
4	2021	Gendarme S, Goussault H, Assié JB, et al. Impact on All-Cause and Cardiovascular Mortality Rates of Coronary Artery Calcifications Detected during Organized, Low-Dose, Computed-Tomography Screening for Lung Cancer: Systematic Literature Review and Meta-Analysis. Cancers (Basel). 2021;13(7):1553	Wrong population
5	2021	Goudemant C, Durieux V, Grigoriu B, et al. Dépistage du cancer bronchique par tomodensitométrie à faible dose: une revue systématique des essais contrôlés randomisés. Rev Mal Respir. 2021 May;38(5):489-505	No critical appraisal of RCT's
6	2021	Barry H. Screening Smokers for Lung Cancer with Low-Dose CT Decreases Lung Cancer Mortality. Am Fam Physician. 2021;103(10):630	No systematic review
7	2021	Rankin N, McGregor D, Donnelly C, et al. Lung Cancer Screening: What is the State of the Evidence about Implementation? Thorac Oncol. 2021; 16(3) S475	Wrong outcome
8	2021	US Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325(10):962-970.	Recommendation statement based on Jonas et al.
9	2022	Li M, Zhang L, Charvat H, et al. The influence of postscreening follow-up time and participant characteristics on estimates of overdiagnosis from lung cancer screening trials. Int J Cancer. 2022;151(9):1491-1501.	Wrong outcome
10	2022	Dawkins P, Lee S, Ye N, et al. Lung Cancer Screening: A Systematic Review of Knowledge Translation Interventions. J Thorac Oncol. 2022 17:9 S167-S168	Wrong outcome



	Year	Publication	Reason for exclusion
11	2022	Lin Y, Hong Y, Lin X, et al. Barriers and facilitators to uptake of lung cancer screening: A mixed methods systematic review. Lung Cancer. 2022;172:9-18.	Wrong outcome
12	2022	Guo L. The Accuracy of Baseline Low-dose CT Lung Cancer Screening: A Systematic Review and Meta-analysis. J Thorac Oncol. 2022 17:9 S184	Wrong outcome
13	2022	Fabbro M, Hahn K, Novaes O, et al. Cost-Effectiveness Analyses of Lung Cancer Screening Using Low-Dose Computed Tomography: A Systematic Review Assessing Strategy Comparison and Risk Stratification. Value in Health 2022 25:12 (S90)	No clinical outcomes
14	2022	Davies M, Vulkan D, Gabe R, et al. Impact of Low Dose CT Screening on Cause of Death in Different Socio-Economic Groups. J Thorac Oncol. 2022;17(9) S190	No systematic review
15	2022	Kunitomo Y, Bade B, Gunderson CG, et al. Racial Differences in Adherence to Lung Cancer Screening Follow-up: A Systematic Review and Meta-analysis. Chest. 2022;161(1):266-275.	Wrong outcome
16	2022	Lin Y, Fu M, Ding R, et al. Patient Adherence to Lung CT Screening Reporting & Data System-Recommended Screening Intervals in the United States: A Systematic Review and Meta-Analysis. J Thorac Oncol. 2022;17(1):38-55.	Wrong outcome
17	2023	Almatrafi A, Thomas O, Callister M, et al. The prevalence of comorbidity in the lung cancer screening population: A systematic review and meta-analysis. J Med Screen. 2023 Mar;30(1):3-13.	Wrong outcome
18	2023	Schwenk A, Laynor G, Leader A. Barriers to lung cancer screening in rural populations: A systematic review. Canc Epidemiol Biomarkers Prev. 2023 32:1	Wrong outcome



Table 101 – Critical appraisal of systematic reviews using the AMSTAR 2 grid

Systematic review	1. PICO components	2. Protocol	3. Study design explanation	4. Comprehensive search strategy	5. Duplicate study selection	6. Duplicate data extraction	7. Details of excluded studies	8. Description of included studies	9. RoB assessment	10. Funding sources	11. Appropriate methods	12. Impact of RoB	13. RoB in discussion	14. Heterogeneity	15. Publication bias	16. Reports conflicts of interest
Agrawal 2023 ²⁸⁶	Green	Red	Green	Orange	Red	Green	Red	Orange	Red	Green	Red	Red	Red	Green	Green	Green
Bonney 2022 ⁵¹	Green	Green	Red	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
Brodersen 2020 ⁷³	Green	Red	Red	Red	Green	Green	Red	Green	Red	Red	Green	Green	Green	Green	Red	Green
Chen 2022 ²⁸⁷	Green	Green	Red	Orange	Green	Green	Red	Green	Green	Red	Green	Green	Red	Green	Green	Green
Ebell 2020 ²⁸⁸	Green	Green	Red	Red	Green	Green	Red	Orange	Green	Red	Green	Green	Red	Green	Green	Green
EUnetHTA 2020 ⁴⁹	Green	Green	Green	Green	Green	Green	Green	Green	Green	Red	Green	Green	Green	Green	Green	Green
Field 2021 ⁶⁰	Green	Green	Red	Red	Green	Red	Green	Orange	Green	Red	Green	Red	Red	Green	Red	Red
Hoffman 2020 ²⁸⁹	Green	Green	Red	Orange	Green	Green	Red	Green	Green	Red	Green	Red	Red	Green	Green	Green
Hunger 2021 ²⁹⁰	Green	Red	Red	Red	Green	Green	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green
Jonas 2021 ⁵⁰	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	N/A	N/A	Green	Green	Red	Green
Passiglia 2021 ²⁹¹	Green	Green	Red	Orange	Green	Green	Red	Green	Green	Red	Green	Red	Red	Green	Green	Green
Sadate 2020 ²⁹²	Green	Green	Red	Orange	Green	Green	Red	Green	Orange	Red	Green	Red	Red	Green	Green	Green

Green color: yes; orange color: partial yes; red color: no.
Abbreviations: N/A = not applicable.



Figure 41 – Update of Bonney et al. (PRISMA flow chart)

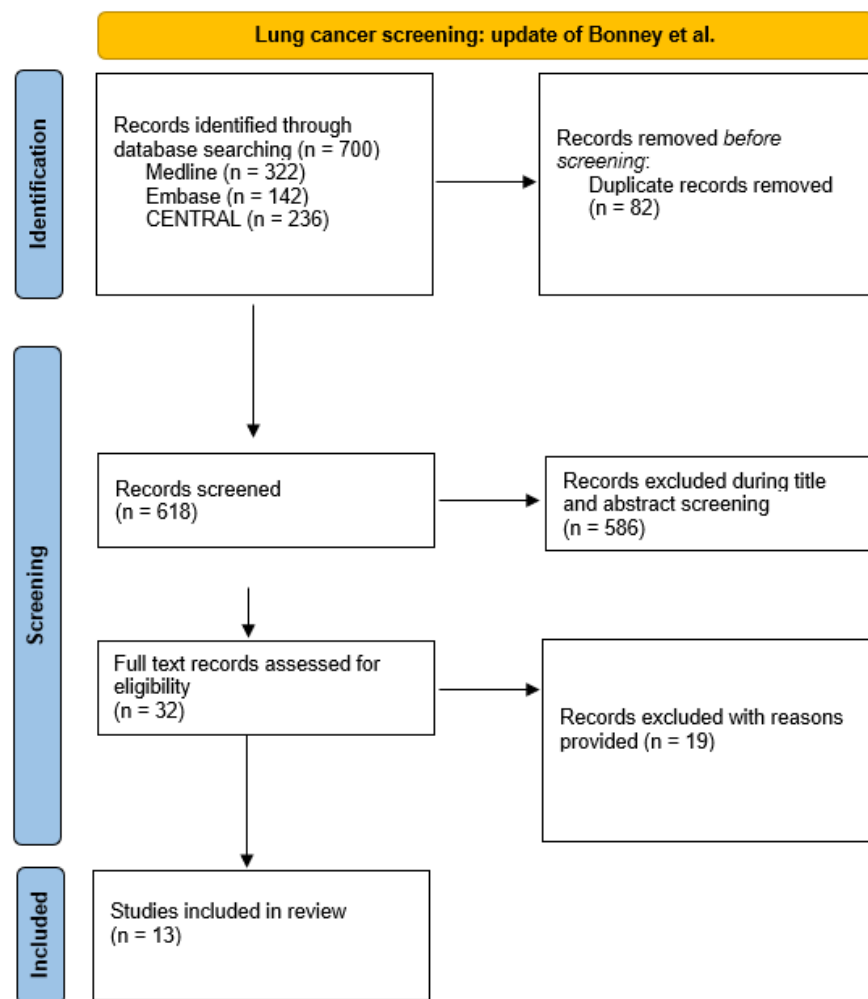


**Table 102 – Included publications of updated systematic review**

Study
NLST
Jassal JS, Grauer JS, Cramer JD. Incidence of Head and Neck Cancer With Lung Cancer Screening: Secondary Analysis of a Randomized Controlled Trial. <i>Laryngoscope</i> . 2022 Aug;132(8):1609-1614.
Kamel MK, Kariyawasam S, Stiles B. Overestimation of screening-related complications in the National Lung Screening Trial. <i>J Thorac Cardiovasc Surg</i> . 2023 Aug;166(2):336-344.e2.
Gareen IF, Gutman R, Sicks J, Tailor TD, Hoffman RM, Trivedi AN, Flores E, Underwood E, Cochancela J, Chiles C. Significant Incidental Findings in the National Lung Screening Trial. <i>JAMA Intern Med</i> . 2023 Jul 1;183(7):677-684.
Su CC, Wu JT, Neal JW, Popat RA, Kurian AW, Backhus LM, Nagpal S, Leung AN, Wakelee HA, Han SS. Impact of Low-Dose Computed Tomography Screening for Primary Lung Cancer on Subsequent Risk of Brain Metastasis. <i>J Thorac Oncol</i> . 2021 Sep;16(9):1479-1489.
NELSON
Sidorenkov G, Stadhouders R, Jacobs C, Mohamed Hoesein FAA, Gietema HA, Nackaerts K, Saghir Z, Heuvelmans MA, Donker HC, Aerts JG, Vermeulen R, Uitterlinden A, Lenters V, van Rooij J, Schaefer-Prokop C, Groen HJM, de Jong PA, Cornelissen R, Prokop M, de Bock GH, Vliegenthart R. Multi-source data approach for personalized outcome prediction in lung cancer screening: update from the NELSON trial. <i>Eur J Epidemiol</i> . 2023 Apr;38(4):445-454.
MILD
Sabia F, Balbi M, Ledda RE, Milanese G, Ruggirello M, Valsecchi C, Marchianò A, Sverzellati N, Pastorino U. Fully automated calcium scoring predicts all-cause mortality at 12 years in the MILD lung cancer screening trial. <i>PLoS One</i> . 2023 May 16;18(5):e0285593
Pastorino U, Boeri M, Sestini S, Sabia F, Milanese G, Silva M, Suatoni P, Verri C, Cantarutti A, Sverzellati N, Corrao G, Marchianò A, Sozzi G. Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial. <i>Ann Oncol</i> . 2022 Apr;33(4):395-405.
ITALUNG
Mascalchi M, Puliti D, Romei C, Picozzi G, De Liperi A, Diciotti S, Bartolucci M, Grazzini M, Vannucchi L, Falaschi F, Pistelli F, Gorini G, Carozzi F, Rosselli A, Carrozzi L, Paci E, Zappa M. Moderate-severe coronary calcification predicts long-term cardiovascular death in CT lung cancer screening: The ITALUNG trial. <i>Eur J Radiol</i> . 2021 Dec;145:110040.
Mascalchi M, Romei C, Marzi C, Diciotti S, Picozzi G, Pistelli F, Zappa M, Paci E, Carozzi F, Gorini G, Falaschi F, Deliperi AL, Camiciottoli G, Carrozzi L, Puliti D. Pulmonary emphysema and coronary artery calcifications at baseline LDCT and long-term mortality in smokers and former smokers of the ITALUNG screening trial. <i>Eur Radiol</i> . 2023 May;33(5):3115-3123.
LUSI
Kaaks R, Christodoulou E, Motsch E, Katzke V, Wielpütz MO, Kauczor HU, Heussel CP, Eichinger M, Delorme S. Lung function impairment in the German Lung Cancer Screening Intervention Study (LUSI): prevalence, symptoms, and associations with lung cancer risk, tumor histology and all-cause mortality. <i>Transl Lung Cancer Res</i> . 2022 Sep;11(9):1896-1911.
AME



Qian F, Zhang Y, Teng J, Wang H, Lou Y, Zhang W, Zhong H, Han B. China Lung Cancer Screening (CLUS) Version 1.0: mortality, Survival and Incidence Rates with Long-Term Follow-up. *Journal of thoracic oncology*, 2022, 17(9), S15-S16.

Rong et al.

Rong F, Shi R, Hu L, et al. Low-dose computed tomography for lung cancer screening in Anhui, China: A randomized controlled trial. *Front Oncol*. 2022;12:1059999.

Li et al.

Li M, Zhang L, Charvat H, Callister ME, Sasieni P, Christodoulou E, Kaaks R, Johansson M, Carvalho AL, Vaccarella S, Robbins HA. The influence of postscreening follow-up time and participant characteristics on estimates of overdiagnosis from lung cancer screening trials. *Int J Cancer*. 2022 Nov 1;151(9):1491-1501.

Table 103 – Updated systematic review: excluded studies with reason for exclusion

Study	Exclusion criterium
Excluded studies after full text evaluation	
Bonney A, Malouf R, Marchal C, Manners D, Fong KM, Marshall HM, Irving LB, Manser R. Impact of low-dose computed tomography (LDCT) screening on lung cancer-related mortality. <i>Cochrane Database Syst Rev</i> . 2022 Aug 3;8(8):CD013829.	Duplicate
Henderson LM, Durham DD, Tammemägi MC, Benefield T, Marsh MW, Rivera MP. Lung Cancer Screening With Low Dose Computed Tomography in Patients With and Without Prior History of Cancer in the National Lung Screening Trial. <i>J Thorac Oncol</i> . 2021 Jun;16(6):980-989.	Described by Bonney et al.
Meza R, Jeon J, Toumazis I, ten Haaf K, Cao P, Bastani M, Han SS, Blom EF, Jonas D, Feuer EJ, Plevritis SK, de Koning HJ, Kong CY. Evaluation of the Benefits and Harms of Lung Cancer Screening With Low-Dose Computed Tomography: A Collaborative Modeling Study for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021 Mar. Report No.: 20-05266-EF-2.	Wrong study design
Hunger T, Wanka-Pail E, Brix G, Griebel J. Lung Cancer Screening with Low-Dose CT in Smokers: A Systematic Review and Meta-Analysis. <i>Diagnostics (Basel)</i> . 2021 Jun 5;11(6):1040.	Already included in search for SR
Manuel L, Fong LS, Ly T, Meredith G. Does lung cancer screening with low-dose computerized tomography improve survival? <i>Interact Cardiovasc Thorac Surg</i> . 2021 Oct 29;33(5):741-745.	Wrong study design
Jonas DE, Reuland DS, Reddy SM, Nagle M, Clark SD, Weber RP, Enyioha C, Malo TL, Brenner AT, Armstrong C, Coker-Schwimmer M, Middleton JC, Voisin C, Harris RP. Screening for Lung Cancer With Low-Dose Computed Tomography: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. <i>JAMA</i> . 2021 Mar 9;325(10):971-987.	Already included in search for SR
Passiglia F, Cinquini M, Bertolaccini L, Del Re M, Facchinetti F, Ferrara R, Franchina T, Larici AR, Malapelle U, Menis J, Passaro A, Pilotto S, Ramella S, Rossi G, Trisolini R, Novello S. Benefits and Harms of Lung Cancer Screening by Chest Computed Tomography: A Systematic Review and Meta-Analysis. <i>J Clin Oncol</i> . 2021 Aug 10;39(23):2574-2585.	Already included in search for SR
de-Torres JP, Wisnivesky JP, Bastarrika G, Wilson DO, Celli BR, Zulueta JJ. Exploring the Impact of Lung Cancer Screening on Lung Cancer Mortality of Smokers With Obstructive Lung Disease: Analysis of the NLST-ACRIN Cohort. <i>Arch Bronconeumol (Engl Ed)</i> . 2021 Jan;57(1):36-41.	Excluded by Bonney et al.



González Maldonado S, Motsch E, Trotter A, Kauczor HU, Heussel CP, Hermann S, Zeissig SR, Delorme S, Kaaks R. Overdiagnosis in lung cancer screening: Estimates from the German Lung Cancer Screening Intervention Trial. <i>Int J Cancer</i> . 2021 Mar 1;148(5):1097-1105.	Described by Bonney et al.
Paci E, Puliti D, Carozzi FM, Carrozzi L, Falaschi F, Pegna AL, Mascialchi M, Picozzi G, Pistelli F, Zappa M; ITALUNG Working Group. Prognostic selection and long-term survival analysis to assess overdiagnosis risk in lung cancer screening randomized trials. <i>J Med Screen</i> . 2021 Mar;28(1):39-47.	Described by Bonney et al.
Gendarme S, Goussault H, Assié JB, Taleb C, Chouaïd C, Landre T. Impact on All-Cause and Cardiovascular Mortality Rates of Coronary Artery Calcifications Detected during Organized, Low-Dose, Computed-Tomography Screening for Lung Cancer: Systematic Literature Review and Meta-Analysis. <i>Cancers (Basel)</i> . 2021 Mar 28;13(7):1553.	Wrong population
Han DH, Duan F, Wu Y, Goo JM, Kim HY, Patz EF Jr. Clinical Significance of Lung-RADS Category 3 Lesions in the National Lung Screening Trial. <i>J Thorac Oncol</i> . 2021 Jul;16(7):1118-1126. doi: 10.1016/j.jtho.2021.02.025.	Described by Bonney et al.
LDCT-SC-FI Low-dose CT Screening for Lung Cancer (NCT05630950) Available from: https://clinicaltrials.gov/show/NCT05630950 , 2022	Wrong intervention
Vogel-Claussen J, Lasch F, Bollmann BA, May K, Kuhlmann A, Schmid-Bindert G, Kaaks R, Barkhausen J, Bohnet S, Reck M. Design and Rationale of the HANSE Study: A Holistic German Lung Cancer Screening Trial Using Low-Dose Computed Tomography. <i>Rofo</i> . 2022 Dec;194(12):1333-1345.	Wrong study design
Agh T, Szilberhorn L, Csanádi M, Széles G, Vokó Z, Ádám G, Kallai Á. A kis sugárdózisú komputertomográfia szerepe a tüdőrákszűrésben [The role of low-dose computed tomography in lung cancer screening]. <i>Orv Hetil</i> . 2022 Sep 11;163(37):1464-1471.	Wrong study design
Agrawal S, Goel AD, Gupta N, Lohiya A. Role of low dose computed tomography on lung cancer detection and mortality - an updated systematic review and meta-analysis. <i>Monaldi Arch Chest Dis</i> . 2022 Jun 21;93(1).	Already included in search for SR
Chen, Y., Zhang, Z., Wang, H. et al. Comparative effect of different strategies for the screening of lung cancer: a systematic review and network meta-analysis. <i>J Public Health</i> . 2022 Feb; 30:2937–2951.	Already included in search for SR
Seo H, Jin KN, Park JS, Kang KM, Lee EK, Lee JY, Yoo RE, Park YJ, Kim JH. Risk of thyroid cancer in a lung cancer screening population of the National Lung Screening Trial according to the presence of incidental thyroid nodules detected on low-dose chest CT. <i>Ultrasonography</i> . 2023 Apr;42(2):275-285.	Wrong study design
Vachani A, Caruso C. Impact of low-dose computed tomography screening on lung cancer incidence and outcomes. <i>Curr Opin Pulm Med</i> . 2023 Jul 1;29(4):232-238. doi: 10.1097/MCP.0000000000000974.	Narrative review

**Table 104 – Incidental findings: search strategy Medline (PubMed)**

Date	June 23, 2023	
Database	Medline (PubMed)	
Search strategy		
1	"Lung Neoplasms"[MeSH] OR "Carcinoma, Non-Small-Cell Lung"[MeSH] OR "Small Cell Lung Carcinoma"[MeSH] OR (("Carcinoma, Squamous Cell"[Mesh] OR "Adenocarcinoma"[MeSH]) AND ("Lung"[MeSH] OR "Lung Diseases"[MeSH])) NSCLC[tiab] OR "lung cancer**"[tiab] OR "lung-cancer**"[tiab] OR "lung malignan**"[tiab] OR "pulmonary Cancer**"[tiab] OR "Pulmonary tumo**"[tiab]	211 513
2	"Mass Screening"[MeSH] OR "Early Detection of Cancer"[Mesh] OR "Early Diagnosis"[MeSH] OR "Tomography, X-Ray Computed"[Mesh] OR "low-dose computed tomography"[tiab] OR "LDCT"[tiab] OR "low-dose computed tomography"[tiab] OR "LDCT"[tiab] OR "CT scan**"[tiab] OR "CAT scan**"[tiab]	739 957
3	"Incidental Findings"[Mesh] OR "incidental**"[tiab]	58 850
4	#1 AND #2 AND #3	519
5	#4 AND ("2019/01/01"[Date - Publication] : "3000"[Date - Publication])	211



Figure 42 – Selection of relevant studies in incidental findings in LDCT screening (PRISMA flow chart)

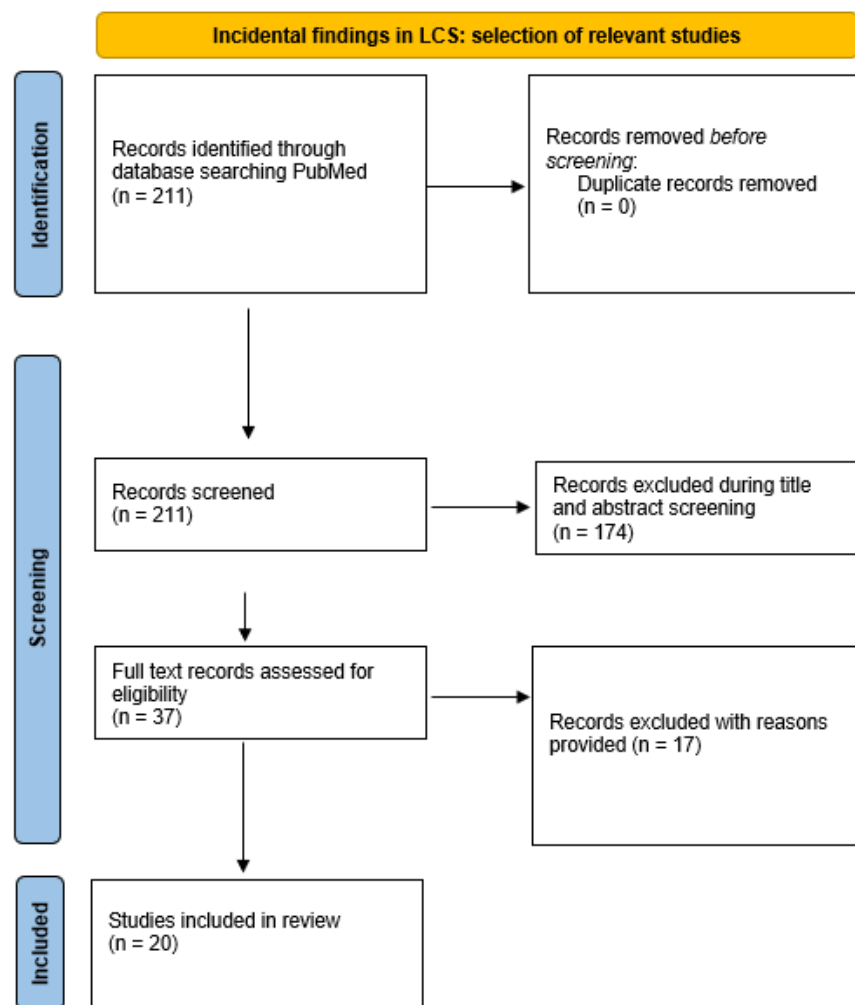



Table 105 – Overview of observational studies reporting on IFs

Author Study Country	N° screens	N° participants	Results on IFs	Categories of IFs
Kinsinger et al. ²⁹³ Veterans Health Administration US	1	2452	41% of participants had one or more incidental findings deemed likely to require followup or further evaluation. The rate of incidental findings deemed likely to need followup varied widely across the eight demonstration sites from 20 to 6%.	Abdominal abnormalities (i.e., mass, cyst, or other finding): 14% Aortic dilation or aneurysm: 8.3% Inflammatory or interstitial processes: 25.4% Thyroid nodules: 2.4%
Wilson et al. ²⁹⁴ PLuSS US	2	3642	4% had “significant” incidental findings, which were not otherwise characterized.	
Morgan et al. ²⁹⁵ Cleveland Clinic US	1	320	94% had some type of incidental abnormality noted by radiologists. 15% had incidental findings categorized as “concerning” and underwent further evaluation.	Calcification of coronary arteries: 56% Calcification of the aorta: 21% Emphysema: 50.6% Aortic dilation: 8.1% Adrenal nodules: 3.8% Renal cysts: 2.5% Thyroid nodules: 4.7%
Swensen et al. ²⁹⁶ Mayo Clinic US	3	1520	14% had incidental nonpulmonary findings of significance that required further evaluation	Abdominal aortic aneurysm: 3.4% Adrenal masses: 2.3% Indeterminate renal masses: 2.2% Renal calculi: 1.6% Breast nodules: 1.1% Non-lung cancers: 0.9%
Janssen et al. ²⁹⁷ LCS Registry Minnesota US	2	1715	Incidental findings were reported in 44% of participants and 40% of screens. Absence of a radiologist’s adjudication of findings.	% of screens: Coronary artery calcification: 22% Incidental lung finding (non specified): 12% Aortic aneurysm: 2% Renal: 0.8% Adrenal: 0.8%



Author Study Country	N° screens	N° participants	Results on IFs	Categories of IFs
			No standards for reporting the extent of incidental lung disease/abnormalities.	Lymphadenopathy: 0.8% Thyroid: 0.7% Pancreas: 0.2% Breast: 0.2% Other clinically significant IF (non specified): 5%
Mendoza et al. ²⁹⁸ Massachusetts General Hospital US	NR	3110	24% of participants were reported to have significant coronary artery calcification (CAC). A change in management (medication change, referral) was observed in 20% of these CAC.	
Kapoor et al. ²⁹⁹ Vanderbilt University Medical Center US	1	1458	138 (9%) of participants had actionable IFs. IFs resulted in additional imaging tests (64%), outpatient clinic visits (27%), and diagnostic procedures (9%)	Renal lesions: 1.5% Dilated thoracic aorta: 1.2% Pulmonary fibrosis: 1.2% Thyroid nodule: 1.1% Lymphadenopathy: 0.9% Hepatic steatosis: 0.7% Adrenal lesion: 0.4% Renal stone: 0.3% Rib fracture: 0.3% Hiatal hernia: 0.3% Valvular calcification: 0.3% Splenic lesion: 0.2% Other: 1.3%
Chen et al. ³⁰⁰ Jiangsu Province Hospital China	1	9826	Incidental pancreatic cystic lesions (PCLs) were identified in 1.75% of high-risk participants, defined using a sex-specific risk score which includes occupational exposure, family history of lung cancer among others.	
Schroeder et al. ³⁰¹	NR	1132	262 (23%) participants had IFs.	Cardiac findings: 16%



Author Study Country	N° screens	N° participants	Results on IFs	Categories of IFs
Augusta Medical Center US			Focus on cardiac findings, which are not well described.	
Bartlett et al. ³⁰² West London pilot UK	1	1145	110 (10%) participants were referred to primary care for IFs. Patient management changes occurred in 23% of referred participants.	Coronary artery calcification: 5.5% Aortic valve calcification: 1.6% Aortic aneurysms: 0.3% Hepatic or renal lesion: 0.3% Other: 1.7%
Mendoza et al. ³⁰³ Massachusetts General Hospital US	NR	3800	331 (8.7%) participants had IFs related to infection or inflammation. The observed opacities were commonly multifocal and 78% resolved on follow-up. Less than 1% were associated with malignancy.	
Regis et al. ³⁰⁴ Lahey Hospital US	5	4301	The rate of significant IFs was 6.4% at baseline and declined with subsequent rounds	No information provided on different IFs
Bradley et al. ⁷⁷ Manchester Lung Health Check pilot UK	2	1409	187 IFs were reported in 161 (11%) participants, of which 8% at baseline. Of 101 (7%) suspected extra-pulmonary cancer findings, eventually 5 (0.35%) malignancies were diagnosed. Coronary artery calcification and emphysema are not included in this analysis. The threshold of significance was at the radiologists' discretion. Clinical management of IFs required 84 specialist reviews (6%), 34 medication changes (2.4%) and 10 interventional treatments (0.71 %).	101 (7%) suspected extrapulmonary cancers: <i>% of participants</i> - Breast: 2% - Hepatic: 1.4% - Renal: 1.3% - Gastro-intestinal: 0.6% - Musculoskeletal: 0.6% - Mediastinal: 0.2% - Laryngeal: 0.1% - Lymphadenopathy: 0.1% - Spinal: 0.1% 86 (6%) other IFs not shown here, but detailed in the article.



Author Study Country	N° screens	N° participants	Results on IFs	Categories of IFs
Hewitt et al. ³⁰⁵ West London pilot UK	2	1853	Interstitial lung abnormalities (ILA) were identified in 78 (4%) participants. The rate of de novo interstitial lung disease (ILD) diagnosis was 1.5%. Disease modifying therapies were commenced in 39% of ILD cases, the majority being antifibrotic therapy.	
Dyer et al. ²⁶⁸ ACR Lung Cancer Screening Registry US	NR	NR	Among 1 695 746 screens (includes baseline and subsequent annual screens) potentially significant IFs were reported in 19% of cases. Part of 'A Quick Reference Guide for Incidental Findings on Lung Cancer Screening CT Examinations', published by the American College of Radiology.	<i>% of all screens:</i> - Coronary arterial calcification: 11.6% - Mass (not specified): 2.8% - Emphysema: 1.2% - Aortic aneurysm: 0.9% - Pulmonary fibrosis: 0.5% - Bronchiectasis: 0.04% - Other: 2.8%
Manyak et al. ³⁰⁶ Virginia Medical Center US	NR	2003	Invasive procedures for clinically important IFs were performed in 19 (0.95%) participants. 13 (0.65%) participants were diagnosed with a non-lung cancer	
Seo et al. ³⁰⁷ Seoul National University Hospital South Korea	1	2329	Incidental thyroid nodules were identified in 4.8% of participants, the incidence of thyroid cancer was 0.8%.	
Henderson et al. ³⁰⁸ North Carolina US	1	4492	IFs were reported in 13.4% of LCS examinations. A specific follow-up was recommended in 3.2% vs no recommended follow-up in 10.2%.	<i>Calculated using Table 2</i> - Coronary artery calcifications: 13.3% (5.2% FU recommended) - Aortic dilatation: 1.7% (0.9% FU recommended) - Emphysema: 9.7% (3.9% FU recommended) - Thyroid nodule: 1.5% (1.2% FU recommended)



Author Study Country	N° screens	N° participants	Results on IFs	Categories of IFs
				- Renal abnormality: 2.4% (1.5% FU recommended) - Hepatic abnormality: 2.1% (1.2% FU recommended) - Bronchiectasis: 4.5% (1.7% FU recommended)
Tisi et al. ⁷⁶ SUMMIT lung cancer screening cohort UK	1	11 115	With a total of 575 IFs referred for primary or secondary care assessment, the number of participants requiring review for clinically relevant findings was 1 in 20. Use of SUMMIT incidental findings management protocol, which includes three categories of referrals. The SUMMIT protocol also includes spirometry as routine for all participants. This publication does not include IFs suspicious for extrapulmonary malignancy, this will be reported in a planned publication. The proportion of participants who actually attended a primary care appointment following referral was relatively low (between 33% and 57%).	Prevalence of non-malignant incidental findings: Emphysema: 33% Brochiectasis: 7.4% Interstitial lung abnormality: 4.8% Coronary artery calcification: 64% Thoracic aortic aneurysm: 2.8% Abdominal aortic aneurysm: 0.02% Aortic valve calcification: 16.3% Osteoporotic wedge fracture: 7.2% Hiatus hernia: 9.6%
Balata et al. ³⁰⁹ Manchester Lung Health Check pilot UK	1	1384	54 (3.9%) of participants were identified as having interstitial lung abnormalities (ILA), 22 (1.6%) were subsequently diagnosed with interstitial lung disease. A mortality rate of 25% at 5 years was observed for ILA.	Only assessing ILA and ILD



APPENDIX 3. SEARCH STRATEGY – ECONOMIC LITERATURE

Table 106 – Search strategy and results for MEDLINE (OVID) and MEDLINE In-Process & Other Non-Indexed Citations (OVID) (Results of 10/01/2023)

Date 10 January 2023			
Publication years 2020 - Current			
Search string	Hits	Search string	Hits
1 exp Economics/	654 536	24 exp Budgets/	14 065
2 Economics, Medical/	9232	25 (econom\$ adj2 (evaluat\$ or analy\$ or study or studies)).ti,ab,kf.	29 761
3 Economics, Nursing/	4013	26 (cost-effectiveness\$ or CEA or cost effectiveness\$).ti,ab,kf.	98 221
4 Economics, Pharmaceutical/	3092	27 (cost-utility\$ or CUA or cost utility\$).ti,ab,kf.	7250
5 exp Economics, Hospital/	25 665	28 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	1 247 136
6 (economic\$ or cost or costs or costly or costing or price or prices or pricing or priced or discount or discounts or discounted or discounting or ration\$ or expenditure or expenditures or budget\$ or afford\$ or pharmacoeconomic\$ or pharmacoeconomic\$).ti,kf.	312 085	29 exp Lung Neoplasms/	268 278
7 (economic\$ or cost or costs or costly or costing or price or prices or pricing or priced or discount or discounts or discounted or discounting or ration\$ or expenditure or expenditures or budget\$ or afford\$ or pharmacoeconomic\$ or pharmacoeconomic\$).ab. /freq=4	138939	30 ((lung\$ or bronch\$ or pulmon\$ or thora\$ or resp\$) adj3 (cancer\$ or neopla\$ or maligna\$ or tumor\$ or tumour\$ or carcinoma\$ or adenocarcinoma\$ or small cell or squamous)).ti,kw.	199 350
8 exp "Fees and Charges"/	31 278	31 (NSLC or NSCLC or SLC or SCLC).ti,kw.	13 367
9 exp "Costs and Cost Analysis"/	261 978	32 29 or 30 or 31	321 117
10 exp Health Care Costs/	71 328	33 ((CT or CAT) adj3 (scan\$ or screen\$)).ti,kw.	9015
11 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ti,ab,kf.	25 083	34 ((compute\$ adj2 tomogra\$) and (scan\$ or screen\$)).ti,kw.	5462
12 exp Decision Support Techniques/	81 902	35 LDCT.ti,ab,ot,kw.	1332
13 exp Models, Economic/	16 168	36 (low-dos\$ adj3 (CT or CAT or compute\$ or tomogra\$)).ti,kw.	2367



14	economic model*.ab,kf.	4044	37	(ultralow-dos\$ adj3 (CT or CAT or compute\$ or tomogra\$)).ti,kw.	62
15	markov\$.tw.	30 197	38	exp Mass Screening/	142 618
16	Markov Chains/	15 880	39	exp "Early Detection of Cancer"/	35 936
17	monte carlo.tw.	56 853	40	33 or 34 or 35 or 36 or 37 or 38 or 39	184 502
18	Monte Carlo Method/	31 841	41	(32 and 40) or (lung adj3 screen\$).ti,kw.	7552
19	(decision adj2 (tree\$ or analy\$ or model\$)).ti,ab,kf.	33 632	42	Animals/ not human.sh.	7 216 171
20	exp Decision Theory/	12 995	43	28 not 42	1 178 529
21	(survival adj3 analy\$).tw.	79 301	44	41 and 43 (920)	920
22	Exp Health Expenditures/	25 526			
23	Uncertainty/	16 945			

Table 107 – Search strategy and results for EMBASE (Results of 10/01/2023)

Date 10 January 2023				
Publication years 2020 - Current				
Search string	Hits	Search string	Hits	
1 'economics'/exp	250 639	16 (('lung*' OR 'bronch*' OR 'pulmon*' OR 'thora\$' OR 'resp\$') NEAR/3 ('cancer*' OR 'malignan\$' OR 'neopla*' OR 'tumor*' OR 'tumour*' OR 'carcinoma*' OR 'adenocarcinoma*' OR 'small cell' OR 'squamous')).ti,kw	267 751	
2 'health economics'/exp	1 013 371	17 ('nslc' OR 'nslcl' OR 'slc' OR 'sclcl'):ti,kw	38 396	
3 ('cost*' NEXT/2 ('effective*' OR 'utility*' OR 'benefit*' OR 'minimi*' OR 'analy*' OR 'outcome' OR 'outcomes')):ti,ab,kw	277 744	18 #15 OR #16 OR #17	506 212	
4 'economic model*':ab,kw	5992	19 (('ct' OR 'cat') NEAR/3 ('scan*' OR 'screen*')):ti,kw	18 162	
5 'markov':ti,ab,kw	36 530	20 (('compute*' NEAR/2 'tomogra*'):ti,kw) AND ('scan*':ti,kw OR 'screen*':ti,kw)	11 070	
6 'monte carlo method'	50 622	21 'LDCT':ti,ab,kw	2521	
7 'monte carlo':ti,kw	19 511	22 ('low-dos*' NEAR/3 ('CT' OR 'CAT' OR 'compute*' OR 'tomogram*')):ti,kw	3936	



8	'decision theory'	2687	23	((('ultralow-dos*') NEAR/3 ('CT' OR 'CAT' OR 'compute*' OR 'tomogram*'))):ti,kw	185
9	'decision tree'	24 812	24	'Mass Screening'/exp	299 277
10	(decision* NEAR/2 (model* OR tree* OR analy*)):ti,kw	10 956	25	'Early Detection of Cancer'/exp	12 171
11	('econom\$' NEAR/2 ('evaluat\$' OR 'analy\$' OR 'study' OR 'studies')):ti,ab,kw	0	26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	335 423
12	('cost-effectiveness*' OR 'CEA' OR 'cost effectiveness*'):ti,ab,kw	144 120	27	(#18 AND #26) OR ('lung' NEAR/3 'screen\$'):ti,ab,kw	16 705
13	('cost-utility*' OR 'CUA' OR 'cost utility*'):ti,ab,kw	10 862	28	#14 AND #27	2346
14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	1 405 136	29	#28 AND ([dutch]/lim OR [english]/lim OR [french]/lim)	2275
15	'lung cancer'/exp	462 419			

Table 108 – Search strategy and results for Econlit (OVID) (Results of 10/01/2023)

Table 166 Search strategy and results for Economic COVID (Results of 10/1/2023)					
Date		10 January 2023			
Publication years		2020 - Current			
Search string		Hits	Search string		Hits
1	Economics.mp.	446 379	16	Lung Cancer.ti,kw.	49
2	(Fees and Charges).mp.	232	17	((lung\$ or bronch\$ or pulmon\$ or thora\$ or resp\$) adj3 (cancer\$ or maligna\$ or neopla\$ or tumor\$ or tumour\$ or carcinoma\$ or adenocarcinoma\$ or small cell or squamous)).ti,tw.	246
3	(Costs and Cost Analysis).mp.	481	18	(NSLC or NSCLC or SLC or SCLC).ti,kw.	3
4	Healthcare Costs.mp.	280	19	16 or 17 or 18	247
5	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,ti,kw.	21 300	20	(Computed Tomography or LDCT or ((CT or CAT) adj3 (screen\$ or scan\$))).ti,ab,kw.	59
6	Decision Support Techniques.mp.	4	21	((compute\$ adj3 tomogra\$) and (scan\$ or screen\$)).ti,ab,kw.	26
7	economic model*.ab,kw.	9116	22	LDCT.ti,ab,kw.	2
8	(econom\$ adj2 (evaluat\$ or analy\$ or study or studies)).ti,ab,kw.	28 939	23	(low-dos\$ adj3 (CT or CAT or compute\$ or tomogra\$)).ti,ab,kw.	2



9	markov\$.tw,ti,ab,kw.	9463	24	(ultralow-dos\$ adj3 (CT or CAT or compute\$ or tomogra\$)).ti,ab,kw.	0
10	monte carlo.ti,kw.	1969	25	Mass Screening.mp	8
11	Health Expenditures.mp.	677	26	Early Detection of Cancer.mp	0
12	Budgets.mp.	3999	27	20 or 21 or 22 or 23 or 24 or 25 or 26	67
13	(cost-effectiveness* or CEA or cost effectiveness*).ti,ab,kw.	3254	28	(19 and 27) or (lung adj3 screen\$).ti,ab,kw.	8
14	(cost-utility* or CUA or cost utility*).ti,ab,kw.	253	29	28 and 15	4
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	498 371			

Table 109 – Search strategy and results for PsycInfo (OVID) (Results of 10/01/2023)

Date 10 January 2023					
Publication years 2020 - Current					
Search string		Hits	Search string		Hits
1	Economics.mp.	38 404	16	Lung Cancer.ti.	1202
2	(Fees and Charges).mp.	273	17	((lung\$ or bronch\$ or pulmon\$ or thora\$ or resp\$) adj3 (cancer\$ or maligna\$ or neopla\$ or tumor\$ or tumour\$ or carcinoma\$ or adenocarcinoma\$ or small cell or squamous)).ti.	1527
3	(Costs and Cost Analysis).mp.	18 711	18	(NSLC or NSCLC or SLC or SCLC). ti,kw.	21
4	Healthcare Costs.mp.	1562	19	16 or 17 or 18	1541
5	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,ti.	27 491	20	(Computed Tomography or LDCT or ((CT or CAT) adj3 (screen\$ or scan\$))).ti,ab.	6554
6	Decision Support Techniques.mp.	1574	21	((compute\$ adj3 tomogra\$) and (scan\$ or screen\$)).ti,ab.	855
7	economic model*.ti.	112	22	LDCT.ti,ab,kw.	37
8	(econom\$ adj2 (evaluat\$ or analy\$ or study or studies)).ti,ab.	5522	23	(low-dos\$ adj3 (CT or CAT or compute\$ or tomogra\$)).ti,ab.	74
9	markov\$.tw,ti,ab.	4679	24	(ultralow-dos\$ adj3 (CT or CAT or compute\$ or tomogra\$)).ti,ab.	0
10	monte carlo.ti.	588	25	Mass Screening.mp	10 785
11	Health Expenditures.mp.	1736	26	Early Detection of Cancer.mp	1677



12	Budgets.mp.	3816	27	20 or 21 or 22 or 23 or 24 or 25 or 26	1877
13	(cost-effectiveness* or CEA or cost effectiveness*).ti,ab.	9241	28	(19 and 27) or (lung adj3 screen\$).ti,ab.	205
14	(cost-utility* or CUA or cost utility*).ti,ab.	729	29	28 and 15	18
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	89 596			

Table 110 – Results of search strategy (second stage)

Database	Identified references
	10 January 2023
MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (via OVID)	920
Embase	2275
EconLit (via OVID)	4
PsycInfo (via OVID)	18
Total (incl. duplicates)	3217
Duplicates	534
Total (excl. duplicates)	2683
Published before 2020 and country ≠ Belgium or the Netherlands*	1986
Total	697

Note: *studies published before 2020 were only excluded if they were not focusing their analyses on Belgium or the Netherlands.

**Table 111 – Excluded studies with reason for exclusion**

Study	Exclusion criterium
Excluded studies after full text evaluation	
Adams SJ, Stone E, Baldwin DR, Vliegenthart R, Lee P, Fintelmann FJ. Lung cancer screening. Lancet (London, England). 2022.	No systematic review (Design)
Allen BD, Schiebler ML, Sommer G, Kauczor HU, Biederer J, Kruser TJ, et al. Cost-effectiveness of lung MRI in lung cancer screening. European Radiology. 2020;30(3):1738-46.	MRI as intervention (Intervention)
Baldwin DR, Callister MEJ. An update on CT screening for lung cancer: The first major targeted cancer screening programme. British Journal of Radiology. 2020;93(1116).	No systematic review (Design)
Bartlett EC, Belsey J, Derbyshire J, Morris K, Chen M, Addis J, et al. Implications of incidental findings from lung screening for primary care: data from a UK pilot. npj Primary Care Respiratory Medicine. 2021;31(1).	No full economic evaluation (Design)
Behar Harpaz S, Weber M, Wade S, Ngo P, Vaneckova P, Sarich P, et al. MA11.03 Updated Cost-Effectiveness Analysis of Lung Cancer Screening for Australia, Capturing Differences in the Impact of NELSON and NLST Outcomes. Journal of Thoracic Oncology. 2022;17(9):S81.	Conference abstract of included published paper (Design)
Behr C, Ijzerman M, Kip MMA, Vliegenthart R, Koffijberg H. EE114 Cost-Utility Analysis of Lung Cancer Screening Combined With Cardiovascular Disease and Chronic Obstructive Pulmonary Disease Screening. Value in Health. 2022;25(12):S75.	Conference abstract (Design)
Behr CM, Koffijberg H, Degeling K, Vliegenthart R, Ijzerman MJ. Can we increase efficiency of CT lung cancer screening by combining with CVD and COPD screening? Results of an early economic evaluation. European Radiology. 2022;32(5):3067-75.	No full economic evaluation (Design)
Behr C, Oude Wolcherink MJ, Ijzerman M, Vliegenthart R, Koffijberg E. POSC55 Model-Based Health Economic Evaluations of Screening Using Chest Computed Tomography: A Systematic Review. Value in Health. 2022;25(1):S96.	Conference abstract (Design)
Bradley SH, Shinkins B, Kennedy MP. What is the balance of benefits and harms for lung cancer screening with low-dose computed tomography? Journal of the Royal Society of Medicine. 2021;114(4):164-70.	No systematic review (Design)
Cheng YC, Lin WY, Lang HC. EE575 Cost-Effectiveness of Low-Dose Computed Tomography Screening for Lung Cancer. Value in Health. 2022;25(12):S169.	Conference abstract (Design)
Chintanapakdee W, Mendoza DP, Zhang EW, Botwin A, Gilman MD, Gainor JF, et al. Detection of Extrapulmonary Malignancy During Lung Cancer Screening: 5-Year Analysis at a Tertiary Hospital. Journal of the American College of Radiology. 2020;17(12):1609-20.	No full economic evaluation (Design)
Crengle S. Comment on: Jaine et al Cost-effectiveness of a low-dose computed tomography screening programme for lung cancer in New Zealand. Lung Cancer 2018, 124, 233–240. 2018/10/01. DOI: 10.1016/j.lungcan.2018.08.004. Lung Cancer. 2020;145:219-20.	Comment (Design)
Cressman S, Tammemagi M, Myers R, Yee J, English J, Mayo J, et al. FP09.01 Economic Impact of Screening Selection with the PLCom2012 Risk Model Versus USPSTF-Guidelines in the International Lung Screening Trial (ILST). Journal of Thoracic Oncology. 2021;16(3):S211-S2.	Conference abstract (Design)
Criss SD, de Koning HJ, Plevritis SK, Meza R, Kong CY. Cost-Effectiveness Analysis of Lung Cancer Screening in the United States. Annals of Internal Medicine. 2020;172(10):706-7.	Response on comment (Design)



Du Y, Sidorenkov G, Heuvelmans MA, Groen HJM, Vermeulen KM, Greuter MJW, et al. Supplementary data for a model-based health economic evaluation on lung cancer screening with low-dose computed tomography in a high-risk population. Data in Brief. 2020;31:105999.	Supplementary data of included article (Design)
Du Y, Li Y, Sidorenkov G, Ye Z, Vliegenthart R, Heuvelmans MA, et al. Cost-effectiveness of lung cancer screening with low-dose computed tomography in China: A modeling study. Journal of Thoracic Oncology. 2021;16(4):S714.	Conference abstract (Design)
Du Y, Li Y, Sidorenkov G, Vliegenthart R, Heuvelmans MA, Dorrius MD, et al. Cost-effectiveness of lung cancer screening by low-dose CT in China: a micro-simulation study. Journal of the National Cancer Center. 2022;2(1):18-24.	General population (Population)
Febbo J, Little B, Fischl-Lanzoni N, Narayan AK, Tiersma KM, Glover M, et al. Analysis of Out-of-Pocket Cost of Lung Cancer Screening for Uninsured Patients Among ACR-Accredited Imaging Centers. Journal of the American College of Radiology. 2020;17(9):1108-15.	No full economic evaluation (Design)
Guan Y, Ren M, Guo D, He Y. [Research Progress on Lung Cancer Screening]. Chinese Journal of Lung Cancer. 2020;23(11):954-60.	Language
Guzman R, Guirao A, Vela E, Cleries M, Garcia-Altes A, Sagarra J, et al. Outcomes and cost of lung cancer patients treated surgically or medically in Catalunya: cost-benefit implications for lung cancer screening programs. European Journal of Cancer Prevention. 2020;29(6):486-92.	No full economic evaluation (Design)
Jaine R, Kvizhinadze G, Nair N, Blakely T. Erratum: Cost-effectiveness of a low-dose computed tomography screening programme for lung cancer in New Zealand (Lung Cancer (2018) 124 (233–240), (S0169500218305208), (10.1016/j.lungcan.2018.08.004)). Lung Cancer. 2020;144:99-106.	Erratum of Jaine (2018). The corrected version is included (Design)
Jensen MD, Siersma V, Rasmussen JF, Brodersen J. Direct and indirect healthcare costs of lung cancer CT screening in Denmark: A registry study. BMJ Open. 2020;10(1).	Comparator is lung function test and no full economic evaluation (Comparator)
McLeod M, Sandiford P, Kvizhinadze G, Bartholomew K, Crengle S. EP01.03-009 Cost-effectiveness of Lung Cancer Screening in New Zealand Varies by Ethnicity. Journal of Thoracic Oncology. 2022;17(9):S175-S6.	Conference abstract (Design)
Morgan H, Baldwin DR. Important parameters for cost effective implementation of lung cancer screening. British Journal of Radiology. 2023;20220489.	No systematic review (Design)
Nagy B, Szilberhorn L, Györbíró D, Moizs M, Bajzik G, Kerpel-Fronius A, et al. EE325 Cost-Effectiveness of Lung Cancer Screening With Low Dose Computed Tomography in Hungary. Value in Health. 2022;25(12):S118.	Conference abstract (Design)
Nagy B, Szilberhorn L, Kerpel-Fronius A, Moizs M, Bajzik G, Voko Z. The budget impact of lung cancer screening with low-dose computed tomography. Orvosi Hetilap. 2021;162(24):952-9.	Language
Ngo PJ, Cressman S, Behar-Harpaz S, Karikios DJ, Canfell K, Weber MF. Applying utility values in cost-effectiveness analyses of lung cancer screening: A review of methods. Lung Cancer. 2022;166:122-31.	No systematic review (Design)
Novellis P, Cominesi SR, Rossetti F, Mondoni M, Gregorc V, Veronesi G. Lung cancer screening: who pays? Who receives? The European perspectives. Translational Lung Cancer Research. 2021;10(5):2395-406.	No systematic review (Design)



Pan X, Dvortsin E, Aerts J, Baldwin DR, Groen HJM, Ramaker D, et al. P1.02-03 Budget Impact Analysis of Volume CT Lung Cancer Screening Based on NELSON Study Outcomes in Europe. <i>Journal of Thoracic Oncology</i> . 2022;17(9):S99.	Conference abstract (Design)
Pan X, Dvortsin E, Baldwin DR, Groen HJM, Ramaker D, Ryan J, et al. EE304 Cost-Effectiveness of Volume Computed Tomography in Lung Cancer Screening: A Cohort Simulation Based on Nelson Study Outcomes. <i>Value in Health</i> . 2022;25(12):S113.	Conference abstract (Design)
Paquete AT, Ryan J, Connolly M, Dance L, Kotsopoulos N. HPR19 Tax Revenue Gains and Societal Net-Monetary Benefit Associated With Implementing Lung Cancer Screening in the United Kingdom. <i>Value in Health</i> . 2022;25(12):S235.	Conference abstract (Design)
Rosell A, Baeza S, Lopez-Segul F, Mouriño R, Saigí M, Munné M, et al. EP01.03-002 Implementation of the International Lung Screen Trial (ILST) in Catalonia: A Cost Analysis study. <i>Journal of Thoracic Oncology</i> . 2022;17(9):S171-S2.	No full economic evaluation (Design)
Schroeder C, Drevets P, Chung JM, Shafer M, Lee R, Berman AE. Potential Financial Impact of Incidental Cardiac Pathology Detected During Lung Cancer Screening. <i>American Surgeon</i> . 2021;87(4):557-60.	No full economic evaluation (Design)
Sudarshan M, Murthy S. Computed tomography screening for lung cancer. <i>General Thoracic and Cardiovascular Surgery</i> . 2020;68(7):660-4.	No systematic review (Design)
Tailor TD, Bell S, Fendrick AM, Carlos RC. Total and Out-of-Pocket Costs of Procedures After Lung Cancer Screening in a National Commercially Insured Population: Estimating an Episode of Care. <i>Journal of the American College of Radiology</i> . 2022;19(1):35-46.	No full economic evaluation (Design)
Thanh NX, Pham TM, Waye A, Tremblay A, Yang H, Dean ML, et al. Expected Cost Savings From Low-Dose Computed Tomography Scan Screening for Lung Cancer in Alberta, Canada. <i>JTO Clinical and Research Reports</i> . 2022;3(7):100350.	No full economic evaluation (Design)
Toumazis I, Erdogan SA, Bastani M, Leung A, Plevritis SK. A Cost-Effectiveness Analysis of Lung Cancer Screening With Low-Dose Computed Tomography and a Diagnostic Biomarker. <i>JNCI Cancer Spectrum</i> . 2021;5(6).	Diagnostic biomarker with screening (Intervention)
Young RP, Hopkins RJ. Cost-effectiveness analysis of lung cancer screening in the United States. <i>Annals of Internal Medicine</i> . 2020;172(10):705-6.	Comment (Design)
Zhao Z, Wang Y, Wu W, Yang Y, Du L, Dong H. Cost-effectiveness of Low-Dose Computed Tomography with a Plasma-Based Biomarker for Lung Cancer Screening in China. <i>JAMA Network Open</i> . 2022.	Diagnostic biomarker with screening (Intervention)
Zhao Z, Du L, Li Y, Wang L, Wang Y, Yang Y, et al. Erratum: Correction: Cost-Effectiveness of Lung Cancer Screening Using Low-Dose Computed Tomography Based on Start Age and Interval in China: Modeling Study (JMIR public health and surveillance (2022) 8 7 (e36425)). <i>JMIR public health and surveillance</i> . 2022;8(10):e43025.	Erratum (Design)
Excluded studies which were included by other systematic reviews (if not included above and published since 2020)	
Kowada A. Cost-effectiveness and health impact of lung cancer screening with low-dose computed tomography for never smokers in Japan and the United States: a modelling study. <i>BMC Pulmonary Medicine</i> . 2022;22(1):19.	Never-smokers (Population)
Jiang B, Linden PA, Gupta A, Jarrett C, Worrell SG, Ho VP, et al. Conventional Computed Tomographic Calcium Scoring vs full chest CTCS for lung cancer screening: a cost-effectiveness analysis. <i>BMC Pulmonary Medicine</i> . 2020;20(1):187.	Computed Tomographic Calcium Scoring (Intervention & Comparator)



APPENDIX 4. TEMPLATE DATA EXTRACTION SHEET FOR ECONOMIC EVALUATIONS

Table 112 – Template data extraction sheet

1	Reference (including all authors)
2	Conflict of interest and/or study funding
3	Country
4	Study question(s)
5	Type of analysis (analytic technique) • e.g., cost-effectiveness analysis, cost-utility analysis,...
6	Design • e.g., Markov model, decision tree,...
7	Population
8	Intervention
9	Comparator
10	Time horizon
11	Discount rate for costs and/or effects
12	Perspective
13	Costs • Cost items included • Measurement of resource use • Valuation of resource use • Data sources • Currency and cost year • Other aspects
14	Outcomes • Endpoints taken into account and/or health states • Valuation of health states • Treatment effect and extrapolation



	• Utility assessment (Quality of Life) • Data sources for outcomes • Other aspects
15	Uncertainty • Scenario analyses • Sensitivity analyses
16	Assumptions
17	Results • Cost-effectiveness and/or cost-utility • Scenario analysis • Sensitivity analysis • Other aspects
18	Conclusion of the authors
19	Remarks



APPENDIX 5. CONFLICTS OF INTEREST STATEMENTS

Table 113 – Full conflict of interest statements

Study	Conflicts of interest	Funding
Behar Harpaz, 2023	The authors declare no competing interests. KC is co-PI of an investigator-initiated trial of cervical screening, Compass, run by the VCS Foundation, which is a government-funded not-for-profit charity; the VCS Foundation has received equipment and a funding contribution from Roche Molecular Diagnostics. She is also co-PI on a major investigator-initiated implementation programme, Elimination of Cervical Cancer in the Western Pacific (ECCWP) which will receive support from the Minderoo Foundation, the Frazer Family Foundation and equipment donations from Cepheid Inc. Neither KC nor her institution on her behalf receives direct funding from industry for any project. KC's research is supported via a National Health and Research Council Australia Leadership Fellowship (NHMRC; APP1194679). KC chairs and participates in a number of advisory committees to government and not-for-profit agencies; no committee participation for commercial companies. MC is an investigator on an investigator-initiated trial of cytology and primary HPV screening in Australia ('Compass') (ACTRN12613001207707 and NCT02328872), which is conducted and funded by the VCS Foundation a government-funded not-for-profit charity. The VCS Foundation has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems. However, neither MC nor his institution on his behalf (The Daffodil Centre, a joint venture between Cancer Council NSW and The University of Sydney) receive direct or indirect funding from industry for Compass Australia or any other project. MW received an honorarium from scientific meeting organisers for a presentation outside the submitted work. MCT developed the PLCOm2012 lung cancer risk prediction model, which is assessed in this study. The model is open access and is available free of charge to noncommercial users. For commercial users, licensing has been assigned to Brock University. MCT has not received any money for the use of the PLCOm2012 model and does not anticipate any payments in the future. KF received travel support from various medical or scientific meeting organisers for participating or being a speaker (or both) and received additional grants or contracts from Olympus and Australian MRFF Next Generation Clinical Researchers	This work is part of the Cancer-Patient Population Projections project (Cancer-PPP) funded by a Medical Research Future Fund (MRFF) Preventive and Public Health Research Initiative: 2019 Target Health System and Community Organisation Research Grant Opportunity, No. MRF1200535. KF is supported by NHMRC/MRFF; HM is supported by NHMRC/MRFF and Metro North HHS. KC is supported by NHMRC. Open Access funding enabled and organized by CAUL and its Member Institutions.



	Programme and MeVis Medical Solutions AG/HealthInc; and payment or honoraria for lectures, presentations, and speaker's bureaus from Willey Cochrane Clinical Answers and is the Chair for Lung Cancer Consultative Group (unpaid) and a Council member.	
Al Khayat, 2022	The authors have no relevant financial or non-financial interests to disclose.	The authors did not receive support from any organization for the submitted work.
Cressman, 2022	The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SC developed the cost-effectiveness model used in the study. The code for the model is available free of charge to non-commercial users, upon request. Commercial users will need to establish an information-sharing agreement with Simon Fraser University and receive approval by the International Lung Screening Trial scientific steering committee. SC has not received money for the use of the economic model and does not anticipate any payments in the future. SC and RMy held grants from Michael Smith Health Research and the Social Sciences and Humanities Council of Canada to support community-engaged research on the topic of access to lung health services. AM received travel or accommodation support for meetings by Roche, Olympus and the International Association for the study of Lung Cancer, KMF received travel support for several medical and scientific meeting organizers and received additional grants or contracts from Olympus and Australian Medical Research Future Fund and MeVis Medical Solutions AG/Health Inc; and payments or honoraria for lectures, presentations or speaker's fees and is the unpaid Chair for Lung Cancer Consultative Group and a Council member. AT received consultancy fees from Olympus Respiratory America and additional grants or contracts from Biodesix Inc and Arch Biomedical Inc.	The International Lung Cancer Screening Trial was funded by the Terry Fox Research Institute, the Vancouver General Hospital and University of British Columbia Hospital Foundation, the BC Cancer Foundation, the Australian National Health and Medical Research Council and the Medical Futures Fund. The funders enabled access to the health services used in the study and in-kind contributions. The funders were not involved in the design, analysis or interpretation of the results of this study.
Gomez-Carballo, 2022	There are no conflicts of interest.	/
Kim, 2022	Conflict of interest relevant to this article was not reported.	This study was supported by a grant from the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (1720310).
Nagy, 2022	Dr Nagy reported receiving grants from János Bolyai scholarship of the Hungarian Academy of Sciences during the conduct of the study. No other disclosures were reported.	The project was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences between 2019 and 2022 (grant number: BO/00824/19/9). Role of Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or



		approval of the manuscript; and decision to submit the manuscript for publication.
Yuan, 2022a	No disclosures were reported.	/
Yuan, 2022b	The authors report no declarations of interest.	No external funding.
Zeng, 2022	The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.	This work was supported by the Hunan Provincial Natural Science Foundation [Grant Number 2021JJ80080].
Zhao, 2022	None declared.	/
Cadham, 2021	Dr Toll has consulted to Pfizer as part of an advisory board on e-cigarettes and testifies as an expert witness on behalf of plaintiffs who have filed litigation against the tobacco industry. Dr Rigotti has consulted for Achieve Life Sciences, which is developing an investigational smoking cessation medication and receives royalties from UpToDate for smoking cessation reviews for clinicians. All other authors report no conflicts of interest.	This work was supported by the National Institutes of Health at the National Cancer Institute (U01CA199284, U01CA199218, R01CA207229, R01CA207078, P30CA016672 and R01CA207228, K99CA241397 to JJ and R35CA197289 to JM) and the Veteran's Health Administration (IIR16-076). The research was also supported in part by the philanthropic contributions to The University of Texas MD Anderson Moon Shots Program. The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.
Diaz, 2021	The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.	This work was partially supported by grants from the Asociacion Española Contra el Cáncer de Barcelona in the 2016 Call for proposals of Research in Oncology [No. PROYBAR16909FU]; the Instituto de Salud Carlos III-ISCIII (Spanish Government) through the project PI19/01118 and CIBERESP [No. CB06/02/0073] (co-funded by Funds/European Regional Development Fund. ERDF, a way to build Europe); and with the support of the Secretariat for Universities and Research of the Department of Business and Knowledge of the Government of Catalonia. Grants to support the activities of research groups (SGR 2017-2019). Grant numbers 2017SGR1718, 2017SGR1085 and



		2017SGR1283. We thank CERCA Programme/Generalitat de Catalunya for institutional support. None of these entities played a role in the study design, data collection, analysis, interpretation of our results, not in the writing of this report or the decision to submit the work for publication.
Esmaeili, 2021	The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.	The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the Tabriz University of Medical Science.
Sun, 2021	None declared.	This work was supported by the National Key R&D Program of China (2017YFC1308700; 2017YFC1308705) and the National Natural Science Fund (general grant: 71673071).
Toumazis, 2021	Dr ten Haaf reported receiving grants from Cancer Research UK, the Horizon 2020 Program of the European Union, and the University of Zurich; personal fees from Erasmus University Medical Center, the International Association for the Study of Lung Cancer, and the Russian Society of Clinical Oncology; and nonfinancial support from the International Association for the Study of Lung Cancer and the Russian Society of Clinical Oncology outside the submitted work. Dr de Koning reported receiving personal fees from Ipsos MORI, Merck Sharp & Dohme, Teva Pharmaceutical Industries, and The Menarini Group outside the submitted work. Dr Plevritis reported receiving personal fees from GRAIL outside the submitted work. No other disclosures were reported.	This study was supported by grants U01CA199284 (Drs de Koning, Meza, Kong, and Plevritis) and U01CA253858 (Drs Gazelle, de Koning, Meza, Kong, and Plevritis) from the National Cancer Institute.
Du, 2020	None declared.	None.
Evans, 2020	None declared.	OncoSim is led and supported by the Canadian Partnership Against Cancer, with model development by Statistics Canada, and is made possible through funding from Health Canada.
Griffin, 2020	The authors declare that they have no competing interests.	This work was supported by The National Institute for Health Research Health Technology Assessment programme (DOI 10.3310/hta22690).
Jaine, 2020	/	This work was supported by the Health Research Council of New Zealand, grant number 10/248.



McLeod, 2020	GK and MM report personal fees from Waitematā District Health Board during the conduct of the study. GK was also a coauthor on the prior CT lung publication (Jaine et al, 2018) and received grants from the NZ Health Research Council outside the submitted work.	This work was supported by the Waitematā and Auckland District Health Boards.
Veronesi, 2020	GV has financial relationships with AB Medica SpA, Johnson & Johnson Medical SpA, and Medtronic Italia SpA, unrelated to the content of this study. NN received a research grant from the Italian National Insurance Institute for Workplace Injuries (INAIL). None of the other authors has any conflict of interest to declare.	/
UK NSC, 2022b	/	/
IHE, 2014	The authors of this publication claim no competing interest.	/

Notes: '/' means no conflicts of interest or funding were disclosed by the authors.



APPENDIX 6. COSTS CONSIDERED IN ACADEMIC PUBLICATIONS (2020-2023) & HTAS

Table 114 – Costs considered in academic publications (2020-2023) & HTAs

Study	Costs	Cost elements
Behar Harpaz, 2023 ¹²² <i>Australia</i>	- AU\$302 - AU\$476 - AU\$861.6 - AU\$62 327 - AU\$69 235 - AU\$63 436 - AU\$56 701 - AU\$38 388 - AU\$6010 - AU\$6010 - AU\$4196 - AU\$2427 - AU\$4606	- Cost of LDCT scan - Cost of follow-up CT - Cost of false positive - Cost of LC management stage I - Cost of LC management stage II - Cost of LC management stage III - Cost of LC management stage IV - Cost of LC management stage “unknown” - Cost of pre-diagnosis stage I - Cost of pre-diagnosis stage II - Cost of pre-diagnosis stage III - Cost of pre-diagnosis stage IV - Cost of pre-diagnosis stage “unknown”
Al Khayat, 2022 ¹²³ <i>The Netherlands</i>	€175 €1109 €638 €15 282 €21 560 €22 240 €23 070 €15 282 €21 560 €22 240 €7800 €6300	- Cost of LDCT scan - Cost of PET scan - Cost of biopsy - Cost of treatment NSCLC stage I (90%S; 5%S+C; 5%S+C+R) - Cost of treatment NSCLC stage II (80%S+C; 20%S+C+R) - Cost of treatment NSCLC stage III (20%S+C; 80%C+R) - Cost of treatment NSCLC stage IV (10%C+R; 30%C+R+I; 60%P) - Cost of treatment SCLC stage I (90%S; 5%S+C; 5%S+C+R) - Cost of treatment SCLC stage II (80%S+C; 20%S+C+R) - Cost of treatment SCLC stage III (20%S+C; 80%C+R) - Cost of treatment SCLC stage IV (10%C+R; 90%P) - Cost of palliative care <i>S = surgery; C = chemotherapy; R = radiotherapy; I = immunotherapy; P = palliative care</i>
Cressman, 2022 ¹²⁴	US\$15	Cost of risk assessment with risk assessment tool for screen-eligible population



<i>Australia & Canada</i>	• US\$6 • US\$6 • US\$450 • US\$202 • US\$238 • US\$204 • US\$135 • US\$326 • US\$0 • US\$22 552 • US\$752 • US\$503 • US\$584 • US\$483 • US\$0 • US\$68 603 • US\$20 868 • US\$9703 • US\$35 111 • US\$10 365 • US\$20 746	• Cost of risk assessment with risk assessment tool for non-eligible population • Cost of assessment with USPSTF eligibility criteria (screen-eligible/non-eligible) • Screening costs 2020 • Cost of baseline LDCT scan (included in screening costs 2020) • Screening costs 2021 • Screening costs 2022 • Screening costs 2023 • Screening costs 2024-2035 • Screening costs 2036-2040 • Curative treatment 2020 • Curative treatment 2021 • Curative treatment 2022 • Curative treatment 2023 • Curative treatment 2024-2033 • Curative treatment 2033-2040 • Non-curative treatment 2020 • Non-curative treatment 2021 • Non-curative treatment 2022-2040 • Progression after curative treatment 2020 • Progression after curative treatment 2021 • Progression after curative treatment 2022-2040
Gomez-Carballo, 2022 ¹²⁵ <i>Spain</i>	• €27.80 • €111.12 • €3.09 • €915.96 • €1829.41 • €5050.88 • €5980.59 • €4218.65 • €5470.75 • €503.59 • €9689.41	• Cost of screening – GP visit (2 foreseen) • Cost of screening – LDCT • Cost of screening – letter+leaflet+phone call • Cost of diagnosis stage I • Cost of diagnosis stage II • Cost of diagnosis stage III • Cost of diagnosis stage IV • Cost of surgery • Cost of chemotherapy • Cost of radiotherapy • Cost of surgery+chemotherapy



	• €10 193 • €5974.34 • €9764.37 • €3989.21 • €835.98 • €7361.27	• Cost of surgery+chemotherapy+radiotherapy • Cost of chemotherapy + radiotherapy • Cost of immunotherapy • Cost of palliative care with hospice • Cost of aftercare • Cost of death
Kim, 2022 ¹²⁶ South Korea	• US\$165 Localized stage • US\$14 026 • US\$6639 • US\$5172 • US\$4242 • US\$3644 • US\$2729 • US\$1963 • US\$1719 Regional stage • US\$18 533 • US\$10 505 • US\$8028 • US\$6338 • US\$5589 • US\$4165 • US\$2929 • US\$2896 Distant stage • US\$18 709 • US\$17 905 • US\$15 890 • US\$13 085 • US\$10 171 • US\$8000	• Cost of screening Localized stage • Index year • Follow-up y1 • Follow-up y2 • Follow-up y3 • Follow-up y4 • Follow-up y5 • Follow-up y6 • Follow-up y7 Regional stage • Index year • Follow-up y1 • Follow-up y2 • Follow-up y3 • Follow-up y4 • Follow-up y5 • Follow-up y6 • Follow-up y7 Distant stage • Index year • Follow-up y1 • Follow-up y2 • Follow-up y3 • Follow-up y4 • Follow-up y5



	• US\$6198 • US\$4812	• Follow-up y6 • Follow-up y7
Nagy, 2022 ¹²⁷ <i>Hungary</i>	• €55.79 • €1.67 • €88.84 • €30.74 • €82.95 • €1559.29 • €1559.29 • €4591.27 • €1394.66 • €7814.32 • €2029.28 • €88.84 • €1559.29 • €2029.28 • €1394.66 • €1449.46 • €1049.34 • €88.84 • €2029.28 • €1394.66 • €1449.46 • €1049.34	• LDCT scan • Invitation cost • Abdominal or chest CT • Bronchoscopy • Transthoracic needle biopsy • Surgery – resection only • Surgery – resection and adjuvant therapy • Chemotherapy – Adjuvant therapy • Radiotherapy – Adjuvant therapy • Chemoradiotherapy – Adjuvant therapy • Chemotherapy – Neoadjuvant therapy and resection • Restaging (Chest CT) – Neoadjuvant therapy and resection • Surgery – Neoadjuvant therapy and resection • Chemotherapy – No resection • Radiotherapy – No resection • Chemoradiotherapy – No resection • Supportive care • Postoperation – no LC – CT scan every 3 months • Postoperation – progressed – Chemotherapy • Postoperation – progressed – Radiotherapy • Postoperation – progressed – Chemoradiotherapy • Postoperation – progressed – Supportive care
Yuan, 2022a ¹²⁸ <i>China</i>	• US\$50.42 • US\$274.62 • US\$2.9 • US\$1.45 • US\$0.58 • US\$1688.52 • US\$1695.12 • US\$2251.01	• Cost of screening – LDCT • Cost of diagnostic test • Cost of human resources in screening • Cost of publicity in screening • Cost of management in screening • Cost of treatment stage I • Cost of treatment stage II • Cost of treatment stage III



	• US\$2741.53	• Cost of treatment stage IV
Yuan, 2022 ¹²⁹ <i>China</i>	• US\$50.42 • US\$1.45 • US\$0.58 • US\$2.9 • US\$274.62 • US\$1688.52 • US\$1695.12 • US\$2251.01 • US\$2741.53 • US\$23.07 • US\$5.77 • US\$1.54 • US\$2.15 • US\$230.72	• Cost of LDCT • Cost of publicity in screening • Cost of management in screening • Cost of human resources in screening • Cost of diagnostic test • Cost of treatment stage I • Cost of treatment stage II • Cost of treatment stage III • Cost of treatment stage IV • Cost of smoking cessation counselling and follow-up • Cost of smoking cessation data management • Cost of smoking cessation telephone charge • Cost of CO monitor and mouthpiece • Cost of smoking cessation drugs
Zeng, 2022 ¹³⁰ <i>China</i>	• US\$55.03 • US\$180.40 • US\$10 264.91 • US\$10 795.86 • US\$11 857.74	• Cost of screening • Confirmation test for positive cases • Cost of treatment localized • Cost of treatment regional • Cost of treatment distant
Zhao, 2022 ¹³¹ <i>China</i>	• CNY245.86 • CNY23.07 • CNY628.36 • CNY1232.44 • CNY47 341.85 • CNY53 344.51 • CNY83 365.95 • CNY90 643.18 • CNY116 471.34	• Direct cost of screening (public advertising, management of screening invitations, salaries of staff members, and depreciation of screening equipment) • Indirect cost of screening (transportation and wages for missed work) • Cost of prediagnosis • Cost of biopsy diagnosis • Cost of carcinoma in situ • Cost of stage I • Cost of stage II • Cost of stage III • Cost of stage IV
Cadham, 2021 ¹³²	• US\$271.44	• Cost of LDCT



<i>The United States of America (USA)</i>	• US\$22.32 • US\$242.28 • US\$361.80 • US\$324.00 • US\$400.68 • US\$393.12 • US\$1410.46 • <i>Not reported</i> • US\$405 • US\$431 • US\$491 • US\$767 • US\$957	• Cost of chest radiograph • Cost of follow-up scans • Cost of bronchoscopy • Cost of mediastinoscopy • Cost of needle biopsy • Cost of VATS • Cost of PET/CT • <i>Lung cancer treatment costs (age-, stage-, and phase-specific)</i> • Pharmacotherapy • Electronic/web-based + pharmacotherapy • Telephone counselling + pharmacotherapy • Group counselling + pharmacotherapy • Individual counselling + pharmacotherapy
Diaz, 2021 ¹³³ <i>Spain</i>	• €175 • €14 160.70 • €26.84 • €343.75	• Cost of LDCT • Post-diagnosis cost • Cost of brief smoking cessation intervention • Cost of intensive smoking cessation intervention <i>More detailed information on costs not provided</i>
Esmaeili, 2021 ¹³⁴ <i>Iran</i>	• IRR 2 436 466 • IRR 77 207 723 • IRR 24 788 126 • IRR 95 011 219 • IRR 36 769 054	• Cost of screening • Cost of curable NSCLC first year • Cost of curable NSCLC second year and beyond • Cost of non-curable NSCLC first year • Cost of non-curable NSCLC second year and beyond
Sun, 2021 ¹³⁵ <i>China</i>	• US\$68 • US\$7984.30 • US\$8158.39	• Cost of screening • Cost of treatment of early-stage lung cancer • Cost treatment of non-early stage lung cancer
Toumazis, 2021 ¹³⁶ <i>The United States of America (USA)</i>	• US\$271.44 • US\$22.32 • US\$242.28 • US\$361.80 • US\$324.00	• Cost of LDCT • Cost of chest radiography • Cost of follow-up scans • Cost of bronchoscopy • Cost of mediastinoscopy



	• US\$400.68 • US\$393.12 • US\$1410.46 • <i>See original publication</i>	• Cost of needle biopsy • Cost of VATS • Cost of PET/CT • Downstream treatment costs by stage and subdivided by phase for each age category
Du, 2020 ¹³⁷ <i>The Netherlands</i>	• €176 • €1908 • €37 909 • €56 556	• Cost of LDCT • Cost of diagnosis • Cost of treatment for stage I-III • Cost of treatment for stage IV
Evans, 2020 ¹³⁸ <i>Canada</i>	• CA\$630 • CA\$67 100	• Cost of smoking cessation intervention • Life time cost of lung cancer treatment
Griffin, 2020 ¹³⁹ <i>The United Kingdom (UK)</i>	• £98.80 • £2.90 • £18.54 • £1.74 • £72.00 • £6.25 • £184.63 • £4589.04 • £5558.14 • £6411.63 • £7279.07 • £6558.14 • £6511.63 • £6046.51 • £5441.86 • £5848.11 • £5359.21 • £5637.60 • £6514.78 • £5415.46 • £4318.07	• Cost of LDCT • Cost of initial invite • Cost of scoring questionnaire and risk stratification • Cost of follow-up letter and LDCT appointment • Cost of GP consultations leading to lung cancer referral • Cost of nurse-led screening consultation • Cost of resourcing following a false positive scan • Cost of end-of-life care for lung cancer patient • Cost of initial diagnosis and treatment if dx stage Ia • Cost of initial diagnosis and treatment if dx stage Ib • Cost of initial diagnosis and treatment if dx stage IIa • Cost of initial diagnosis and treatment if dx stage IIb • Cost of initial diagnosis and treatment if dx stage IIIa • Cost of initial diagnosis and treatment if dx stage IIIb • Cost of initial diagnosis and treatment if dx stage IV • Cost of index year diagnosis, treatment, and follow-up if dx stage Ia • Cost of index year diagnosis, treatment, and follow-up if dx stage Ib • Cost of index year diagnosis, treatment, and follow-up if dx stage IIa • Cost of index year diagnosis, treatment, and follow-up if dx stage IIb • Cost of index year diagnosis, treatment, and follow-up if dx stage IIIa • Cost of index year diagnosis, treatment, and follow-up if dx stage IIIb



	• £2787.31	• Cost of index year diagnosis, treatment, and follow-up if dx stage IV
Jaine, 2020 ¹⁴⁰	• NZ\$722.80	• Cost of LDCT
New Zealand	• NZ\$30.33	• Cost per person invited (time to identify eligible candidates; invitation)
	• NZ\$500	• Cost of incidental finding
	• NZ\$1836.65	• Cost of diagnostic test (60% CT guided biopsy; 20% bronchoscopy; 20% endobronchial ultrasound)
	• NZ\$2835.96	• Cost of complication from diagnostic test
	• Not reported	• Cost of treatment per stage
	• Not reported	• Average health system costs
McLeod, 2020 ¹⁴¹	• NZ\$400	• Cost of LDCT
New Zealand	• NZ\$30	• Cost per person invited
	• NZ\$1837	• Cost per diagnostic test
	• NZ\$500	• Cost of incidental findings
	• NZ\$2835	• Cost of major complications
	• Not reported	• Cost of treatment per stage
	• Not reported	• Health system costs
Veronesi, 2020 ¹⁴²	• €80	• Cost of LDCT
Italy	• €28 022	• Cost of treatment stage IA
	• €26 772	• Cost of treatment stage IB
	• €22 776	• Cost of treatment stage II
	• €33 343	• Cost of treatment stage III
	• €39 064	• Cost of treatment stage IV
	• €2007	• Cost of false positive workup
UK NSC, 2022b ¹¹⁶	• £77.31	• Cost of LDCT
The United Kingdom (UK)	• £0.66	• Cost of pre-invitation notice
	• £0.79	• Cost of invitation letter for participation
	• £0.84	• Cost of invitation reminder
	• £7.62	• Cost of telephone triage call
	• £0.70	• Cost of invitation letter for screening appointment
	• £116.81	• Cost of multidisciplinary team meeting
	• £77.31	• Cost of further CT scan



• £151.13	• Cost of out-patient follow-up
• £665.58	• Cost of PET scan
• £724.09	• Cost of needle biopsy
• £57.00	• Cost of surgical referral
• £973.56	• Cost of endobronchial ultrasound (EBUS)
• £59.50	• Cost of oncology referral
• £5094	• Treatment cost of stage I – diagnosis
• £15 834	• Treatment cost of stage I – recurrence
• £392	• Treatment cost of stage I – ongoing
• £5 537	• Treatment cost of stage II – diagnosis
• £24 220	• Treatment cost of stage II – recurrence
• £392	• Treatment cost of stage II – ongoing
• £17 999	• Treatment cost of stage III – diagnosis
• £14 831	• Treatment cost of stage III – recurrence
• £401	• Treatment cost of stage III – ongoing
• £16 456	• Treatment cost of stage IV – diagnosis
• £5382	• Treatment cost of stage IV – recurrence
• £422	• Treatment cost of stage IV – ongoing

Unit costs (see original publication for rates of consumption)

- £42
- £115
- £303
- £146
- £130
- £652
- £749
- £181
- £4357
- £6303

Cost elements of LC diagnosis & treatment by stage:

- Diagnostics & Imaging: Chest X-ray
- Diagnostics & Imaging: Contrast enhanced chest, lower neck, and abdomen CT
- Diagnostics & Imaging: PET-CT
- Diagnostics & Imaging: Spirometry
- Diagnostics & Imaging: TLCO test
- Diagnostics & Imaging: Flexible bronchoscopy (no EBUS)
- Diagnostics & Imaging: EBUS-guided TBNA plus or minus bronchoscopy
- Diagnostics & Imaging: CT biopsy
- Surgery: Elective - Lobectomy, wedge resection, pneumonectomy, segmental resection, sleeve resection
- Surgery: Emergency - Lobectomy, wedge resection, pneumonectomy, segmental resection, sleeve resection



	• £1515 • £7720 • £3084 • £3999 • £3440 • £917 • £5505 • £3832 • £8743 • £12 576 • £1506 • £2372 • £1844 • £5869 • £18 859 • £32 699 • £23 901 • £13 788 • £3063 • £41 149 • £55 090 • £87 630 • £28 451 • £42 756 • £55 290	• Surgery: Airway stents for endobronchial obstruction • Surgery: Endobronchial debulking • Radiotherapy: Intracranial procedures • Radiotherapy: RT for curative intent (SABR) • Radiotherapy: RT for curative intent (non-SABR) • Radiotherapy: Palliative RT • Chemo-radiotherapy: Curative intent • Chemotherapy: Docetaxel monotherapy • Chemotherapy: Docetaxel plus nintedanib • Chemotherapy: Pemetrexed maintenance • Chemotherapy doublet: Platinum + vinorelbine • Chemotherapy doublet: Gemcitabine + carboplatin • Chemotherapy doublet: Gemcitabine + cisplatin • Chemotherapy doublet: Pemetrexed + platinum • Immunotherapy: Pembrolizumab • Immunotherapy: Durvalumab • Chemo-immunotherapy: Pembrolizumab + carbo/cis + gem/pemetrexed • TKI: Gefitinib • TKI: Erlotinib • TKI: Entrectinib • TKI: Crizotinib • TKI: Alectinib • TKI: Osimertinib • TKI: Afatinib • TKI: Brigatinib
IHE, 2014 ¹¹⁸ Canada	• CA\$81.00 • CA\$30.70 • CA\$88.44 • CA\$30.70 • CA\$163.11 • CA\$219.87 • CA\$1583.05	• Cost of LDCT • Cost of physician recruitment • Cost of screening test implementation • Cost of communicating screen result • Cost consultation for positive test • Cost of non-invasive diagnostic procedures for positive screen • Cost of invasive diagnostic procedures for positive screen



See original publication for detailed costs of LC diagnosis & treatment by stage and cost type

Included cost elements for LC diagnosis & treatment by stage and cost type:

- Pre-diagnosis (GP)
 - Diagnosis (specialist)
 - Chemotherapy (neo-adjuvant, adjuvant, first line, second line, third line)
 - Chemo- and radiotherapy (neo-adjuvant, concurrent)
 - Surgery
 - Palliative radiotherapy
 - Prophylactic cranial irradiation
 - Surveillance (year 1-5)
 - Cured
 - Supportive care only (palliative radiotherapy)
 - Supportive care only (ongoing care)
 - End-of life care (3 months, 2 months, 1 month before death)
-

Notes: Indicative currency exchange rates on 31/05/2023: AU\$1 = €0.61; US\$1 = €0.94; CNY1 = €0.13; IRR1 = €0.000022; £1 = €1.16; NZ\$1 = €0.56; CA\$1 = €0.69. This report refers to the original studies for the authentic sources used for costs.



APPENDIX 7. FACTORS CONSIDERED IN SENSITIVITY ANALYSES OF INCLUDED ECONOMIC STUDIES

Table 115 – Factors considered in sensitivity & scenario analyses

Study	Type of sensitivity analysis performed	Main parameters & assumptions tested (parameters in bold are considered to have a substantial impact on the ICER*)
Behar-Harpaz, 2023	• Deterministic • Probabilistic	<u>Sensitivity analyses:</u> • Screening mortality benefit • Mortality benefit after screening phase • Lung cancer hazard ratio • Disutilities of screening, follow-up, false positives • Cost of LDCT screen • Rate of overdiagnosis • All-cause mortality hazard ratio • Utility weights • Cost of LC treatment • Cost of stage IV treatment • Cost of false positive • Rate of false positives • Rate of follow-up CT scans • Stage shift (only costs and disutilities, not mortality) • Stage 'unknown' composition • 5-year survival (only costs and disutilities, not mortality) • Cost pre-diagnosis in screening scenario • Smoking cessation rates <u>Scenario analyses:</u> • Selection criteria (PLCom2012, USPSTF2021) • Time horizon
Al Khayat, 2022	• Deterministic • Probabilistic	<u>Sensitivity analyses:</u> • Transition probabilities • LC prevalence



		• Costs • Utilities <i>Insufficient data was available to estimate the impact of the individual parameters</i> <u>Scenario analyses:</u> • Start & stop age
Cressman, 2022	• Deterministic • Probabilistic	• Risk threshold (PLCO_{m2012}) • Male and female incidence • Male and female mortality • Discount rate • Cost of non-curative treatments • Transition probabilities • Health utilities
Gomez-Carballo, 2022	• Deterministic • Probabilistic	<u>Sensitivity analyses:</u> • Cost of treatment • Cost of diagnosis • Cost of screening • High-risk population size <u>Scenario analyses:</u> • Time horizon • Discount rate • Participation/adherence rate • Probabilities • Utilities
Kim, 2022	• Deterministic	<u>Sensitivity analyses:</u> • Positive rates • Distribution of SEER summary stages • Distribution by age group • Costs by SEER summary stage • Costs of distant stage • Screening costs • Utilities by SEER summary stage • Utilities of screening subjects



		• Mortality by SEER summary stage • Mortality due to other diseases • Screening interval (biennial) • Discount rates
		<u>Scenario analyses:</u> • Start & stop age
Nagy, 2022	• Deterministic • Probabilistic	<u>Sensitivity analyses:</u> • Utility of no lung cancer post-operation • LDCT screening cost • Costs after progression • Proportion of IA among diagnosed, no screening • Probability of clinical detection • Cost of progressed cases post-operation • Proportion of IB among diagnosed, no screening • Initial prevalence • No lung cancer utility • Proportion of IIIA among screen-detected cases, yearly screens • Death after no resection • Utility after progression • Proportion of progressed cases after operation at stage IB • Examination utility • Proportion of progressed cases after operation at stage IIA • Proportion of IIA among screen-detected cases, yearly screens • Proportion of resections carried out at stage IIA • Proportion of IIA among diagnosed, no screening • Negative first yearly screen – false negative • Cost of no lung cancer post-operation • Proportion of progressed cases after operation at stage IA • Cost of resection and adjuvant therapy • Proportion of IIIB among screen-detected cases, yearly screens • Proportion of IV among screen-detected cases, yearly screens • Costs of treatment without resection



		<u>Scenario analyses:</u> • Start age • Screening frequency • General population eligible
Yuan, 2022a	• Deterministic • Probabilistic	<u>Sensitivity analyses:</u> • Discount rate • Health utility of stage I LC patient • Health utilities of other LC stages • Cost of LDCT scan • Cost of diagnostic test • Cost of treatment for different stages • Cost of human resources in screening • Cost of publicity in screening • Cost of management in screening • Screening compliance • Age-specific incidence • RR of LC incidence in heavy smokers compared with total population • Overdiagnosis rate • LC stage-specific annual probability of death • Stage distribution with screening • Stage distribution without screening • Specificity LDCT scan • Sensitivity LDCT scan • Excess RR of LC per screening <u>Scenario analyses:</u> • Start age
Yuan, 2022b	• Probabilistic	<u>Sensitivity analyses:</u> • Discount rate • Overdiagnosis rate • Smoking cessation intervention RR • Specificity of LDCT scan • Sensitivity of LDCT scan



		• Screening compliance • LC stage-specific annual probability of death • Stage distribution with screening • Stage distribution without screening • Excess RR of LC per screening round • Health utilities of different LC stages • Cost of LDCT scan • Cost of publicity • Cost of management • Cost of human resources • Cost of diagnostic test • LC treatment cost • Smoking cessation costs <i>Insufficient data was available to estimate the impact of the individual parameters</i> <u>Scenario analyses:</u> • Start age • Smoking duration (PY)
Zeng, 2022	• Deterministic • Probabilistic	• Discount rate • Overdiagnosis rate • Health state utility for localized LC • Health state utility for regional LC • Cost of LDCT screening • Sensitivity of LDCT scan • Specificity of LDCT scan • Cost of confirmation test • Treatment costs for each state
Zhao, 2022	• Deterministic	<u>Sensitivity analyses:</u> • Incidence rate of heavy smokers • Specificity of LC • Sensitivity of LC • Cost of LDCT • CPI rate



		- Discount rate - Cost of maintenance
		<u>Scenario analyses:</u> - Start age - Screening interval
Cadham, 2021	One-way and two-way	Screening coverage Intervention costs
Diaz, 2021	- Deterministic - Probabilistic	<u>Sensitivity analyses:</u> Screening coverage Smoking cessation coverage Smoking cessation cost Screening cost Smoking cessation & screening cost Sensitivity of screening Sensitivity of smoking cessation & screening Smoking cessation effectiveness - Survival Post-diagnosis cost <u>Scenario analyses:</u> - Screening interval - Start & stop age
Esmaeili, 2021	- Deterministic - Probabilistic	- Cost of health states - Screening cost - Incidence of LC in smokers - Transition probabilities - Health state utilities Overdiagnosis rate - Sensitivity - Specificity
Sun, 2021	Deterministic (univariate and multivariate)	<u>Sensitivity analyses:</u> Sensitivity



		• Specificity • Overdiagnosis rate <u>Scenario analyses:</u> • Start age
Toumazis, 2021	• Deterministic • Probabilistic	<u>Sensitivity analyses:</u> • Health utility of stage I NSCLC • Health state utilities of other stages • LDCT cost • Cost of follow-up scans • Cost of bronchoscopy • Cost of mediastinoscopy • Cost of needle biopsy • Cost of VATS • Cost of PET/CT • Cost of downstream treatment • Ineligibility of individuals with short life expectancy (<5 years) <u>Scenario analyses:</u> • Start age • Amount of pack years – eligibility • Time since quitting – eligibility
Du, 2020	• Deterministic	<u>Sensitivity analyses:</u> • Lifetime risk • Specificity • Attendance rate (impact only considerable in male heavy smokers) • Self-detected diameter, log-transformed • Mean age of incidence • Screening cost • Diagnostic cost • Treatment cost stage I-III • Treatment cost stage IV <u>Scenario analyses:</u> • Start and stop age



		Screening frequency
Evans, 2020	- Deterministic - Probabilistic	Quit rate per attempt Cessation intervention cost per attempt - Recruitment rate - Adherence rate
Griffin, 2020	- Deterministic - Probabilistic	<u>Sensitivity analyses:</u> - Proportion of those receiving risk prediction who are men - Population mean age - Population standard error - Participation rate Natural history of LC Survival from diagnosis Other cause mortality - Risk prediction - Screening effectiveness - Quality of life - Disutility (& duration) associated with false positive - Disutility (& duration) associated with anxiety Screening cost - Cost of false positive - Cost of diagnosis Cost of treatment - Risk threshold <u>Scenario analyses:</u> - Screening interval - Start & stop age - Discount rate
Jaine, 2020	- Deterministic - Probabilistic	<u>Sensitivity analyses:</u> Cost of screening - Cost of diagnosis - Screening coverage



		• Lead time • Invitation cost • Incidental findings (number & cost) • Stage distribution at start of screening • Screening sensitivity • Screening specificity • Complication rate • Diagnostic testing adherence rate • Incidence of LC in eligible population • Incidence of LC in non-eligible population <u>Scenario analyses:</u> • Start & stop age • Only current smokers • Maori and non-Maori population • Discount rate
McLeod, 2020	• Deterministic • Probabilistic	• Screening cost • Cost of diagnosis • Diagnosis adherence • Lead time • Invitation cost • Smoking cessation rate • Complication rate & costs • Overdiagnosis • Incidence of LC • Screening sensitivity • Screening specificity • Health system costs • Background mortality & morbidity • Cost and number of incidental findings <i>None of the parameters had a considerable impact on ICER.</i> <u>Scenario analyses:</u> • Maori vs non-Maori inputs



		• Start & stop age • Male vs female • Discount rate • Screening coverage
Veronesi, 2020	• Deterministic • Probabilistic	• Prevalence of LC • Screening sensitivity • Screening specificity • Screening cost • LC treatment cost stage IA • LC treatment cost stage IV • LC treatment cost other stages • Cost of false positive • Life expectancy stage IA • Life expectancy other stages • Lead time bias by stage
UK NSC, 2022b	• Deterministic • Probabilistic	• Deterministic: each parameter • Risk threshold • Start & stop age • Screening interval • Incidence of LC • Population age distribution • Accuracy of risk prediction • Participation rate • Tumour growth rate • Survival gain due to early diagnosis • Disutility due to screening or diagnosis anxiety • Disutility due to metastatic progression • Social care costs • End of life costs • Screening cost • Time horizon • Discount rate



		• No 3 month CT of indeterminate cases • Population age
IHE, 2014	• Deterministic	• Participation rate • Phase-in period

Note: * a considerable impact was defined as a 20% change in the base case ICER or more.

Table 116 – Conclusions of academic publications (2020-2023) & HTAs

Studies	Authors' conclusions
Academic publications	
Behar Harpaz, 2023 ¹²²	Our results suggest that lung cancer screening with LDCT could be cost-effective in the Australian setting, dependent on achieving the mortality benefit observed in international trials. These findings contributed to a recent evaluation by the Australian Medical Services Advisory Committee, which in October 2022 recommended the establishment of a national screening programme in Australia. The effective implementation of a potential programme, and how well it is accepted and adopted by local health systems and high-risk communities, will be critical to its effectiveness and cost-effectiveness.
Al Khayat, 2022 ¹²³	In this study, we showed that lung cancer screening is cost-effective in a population of smokers and ex-smokers. Screening of almost all age groups of smokers and ex-smokers resulted in cost-effectiveness ratios under the €20,000 per QALY gained threshold. This implies that lung cancer screening of smokers and ex-smokers is cost-effective in The Netherlands. Notably, screening start and stop age has significant impact on the cost-effectiveness of screening scenarios. Increasing the start age reduced the cost and benefits of lung cancer screening, while starting screening at younger age increased the cost and benefits of lung cancer screening. Our study indicated that lung cancer screening program for smokers and ex-smokers is cost-effective in the Netherlands. Our results may support policy makers and guideline developers who face the decision whether lung cancer screening should be implemented for smokers and ex-smokers.
Cressman, 2022 ¹²⁴	The PLCom2012 model saved costs, increased QALYs and mitigated socioeconomic and sex-based disparities in access to screening.
Gomez-Carballo, 2022 ¹²⁵	This CEA of an LC SP in a high-risk Spanish population has shown that the SC is a cost-effective alternative compared to the NS from the NHS perspective. It resulted in an ICER of €2345/QALY gained over the patients' lifetime assuming a 70% presentation rate in 3 screening rounds. The SC was more effective (4.80 QALY/patient gained) and meant an additional investment (€11 264€/patient) mainly caused by the screening cost added to the programme. Sensitivity analyses indicate that the obtained results are robust in terms of changes in the presentation rates, costs and cost-effectiveness thresholds.
Kim, 2022 ¹²⁶	In conclusion, our results support the adoption of annual LDCT screening for lung cancer in heavy smokers. The base case (aged 55-74) showed the cost-effectiveness of the lung cancer screening program but the scenario targeting age between 60 and 74 years would be the most cost-effective in the context of Korea. Considering the economic benefits of lung cancer screening and



	the high incidence and mortality of lung cancer, annual LDCT screening with a target age of 60 years and above may be a favorable choice in countries with high disease burden due to lung cancer.
Nagy, 2022 ¹²⁷	Introducing nationwide LC screening with LDCT for the high-risk target group could be cost-effective. Our study indicates the importance to design screening for the appropriate risk groups and treating screening programs with a mid- and long-term focus. Finally, to refer to the title of this article, our analysis aimed to answer the question from the perspective of cost-effectiveness only. Organizational, implementation, and capacity issues need to be handled adequately, as well as effective and sustained participation of the target population to get a definite “yes” to the question we raised.
Yuan, 2022a ¹²⁸	In conclusion, in heavy smokers, implementing lung cancer screening with LDCT is cost effective and can be conducive to early diagnosis and early treatment of patients. We recommend that the optimal age to start screening is 50 years old. High-risk population can be identified through inquiry into their smoking history and age. Through explanation on the screening significance, we may encourage patients to participate in if they meet the inclusion criteria. At the same time, it may also be beneficial to further explore the feasibility of post setting for nursing navigators in China to reduce screening barriers for participants.
Yuan, 2022b ¹²⁹	In conclusion, the present study suggests that screening for high-risk groups of lung cancer in China could be cost-effective. The combination of nurse-led smoking cessation intervention and screening can greatly improve the health and economic effect. More professional nurses who can provide smoking cessation intervention for patients should be involved in the lung cancer screening program. The criteria for lung cancer screening (with nurse-led smoking cessation intervention) should be targeted at people who are over 45 years and have at least 20 pack-year smoking history; and for screening alone should be over 50 years and 20 pack-year smoking history.
Zeng, 2022 ¹³⁰	Under a willingness-to-pay (WTP) threshold of three times the Chinese gross domestic product (GDP) per capita (US \$37,654), annual screening with an initiating age at 50 was most cost-effective in both male and female cohorts. By taking into account both the national healthcare expenditures and the effect of LDCT screening, our study results support undertaking LDCT screening annually from 50 years old in general populations.
Zhao, 2022 ¹³¹	This economic evaluation revealed that a population-based lung cancer screening program in China for heavy smokers using LDCT could result in more QALYs, although with greater expense than nonscreening. Using the WHO threshold for cost-effectiveness analysis, the annual screening strategy from 55 to 74 years and one-time screening strategy from 65 to 74 years can be considered cost-effective. Moreover, annual screening was the most promising; thus, annual screening should be promoted in China to realize actual benefits.
Cadham, 2021 ¹³²	Providing smoking cessation at the point of lung cancer screening reduces lung cancer cases and deaths and increases life expectancy. All of the interventions we evaluated provided benefits at reasonable costs (67). Selection of specific cessation interventions will depend on implementation and dissemination considerations, including the prevalence of smoking in the lung cancer screening-eligible population, individual choices of screen-eligible smokers, the feasibility of implementation, and local resources.
Diaz, 2021 ¹³³	As indicated by the WHO, 90% of lung cancers could be avoided by eliminating tobacco use[50]. However, screening with LDCT is the only approach to avoid mortality of those who already have a high risk of cancer. A long-term organized approach combining primary prevention with smoking cessation interventions and secondary prevention with LDCT screening would result in a large decrease in the burden of lung cancer in the near future. These combined prevention strategies, especially when providing several intensive interventions for smoking cessation at early ages, are more cost-effective than both approaches separately and allow for



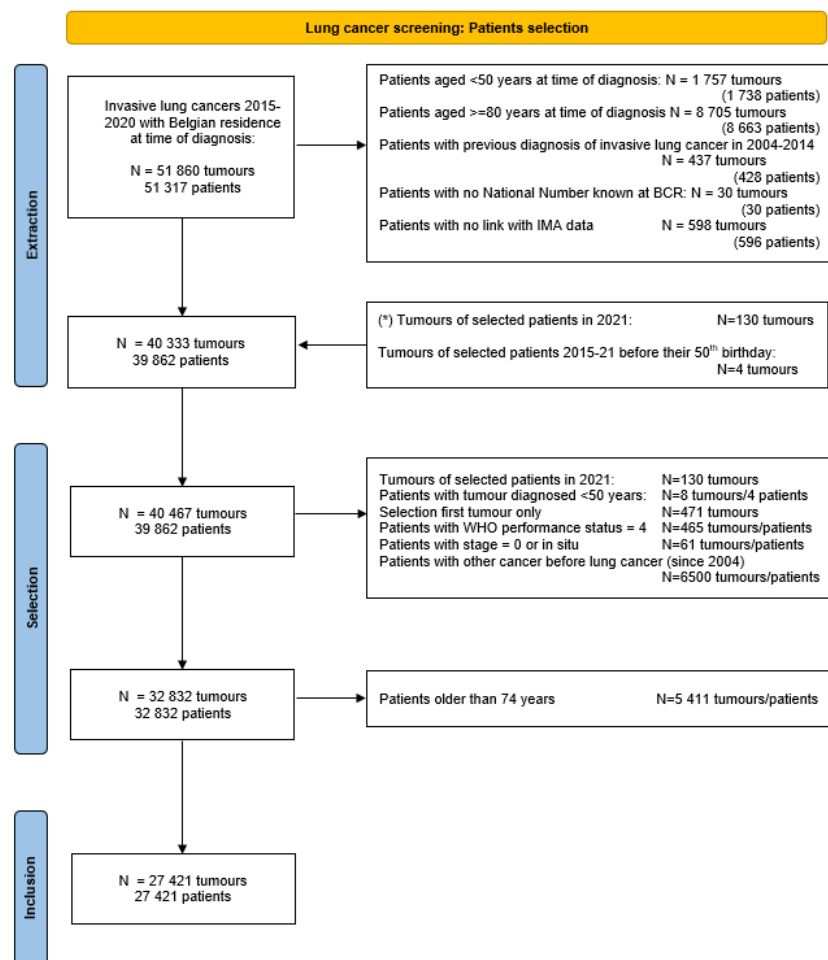
	a more intensified LDCT screening without losing efficiency. Spain is currently in the IV phase of the epidemic curve and shows similar behaviour to the rest of the countries of southern Europe[45]. The similarity in the regions anticipates that these results will also be of more general interest. It is of vital importance to allocate resources efficiently at a time of health and economic crisis like now, where health policymakers must decide in circumstances of large uncertainty and face difficult trade-offs given the health, economic and social challenges that arise.
Esmaeili, 2021 ¹³⁴	The findings of this study suggest that implementing screening by LDTC is cost-effective in patients with LC, and is recommended for inclusion in Iranian treatment guidelines.
Sun, 2021 ¹³⁵	In summary, we can conclude that annual LDCT screenings among high-risk smokers (>20 pack-years) in urban areas of China are likely to be cost-effective. However, the effectiveness depends on the performance of the screening strategy. Among the five screening strategies, screening from the initial age of 55 years is found to be the most cost-effective.
Toumazis, 2021 ¹³⁶	This economic evaluation found that the 2021 USPSTF recommendation for lung cancer screening was cost-effective when directly compared with the 2013 USPSTF recommendation. However, the cost-effectiveness of lung cancer screening may be improved if screening coverage is expanded to include former smokers with 20 pack-year smoking histories who have not smoked for more than 15 years; this expansion of screening eligibility warrants further consideration.
Du, 2020 ¹³⁷	In conclusion, the results from a microsimulation model show that lung cancer screening with LDCT is cost-effective in a high-risk population. At a cost-effectiveness threshold of 60 k€/LYG, the optimal screening scenario for male heavy smokers is annual screening from 55 to 80 years old, yielding a cost of 27.6 k€/LYG and 15.9% mortality reduction of lung cancer relative to no screening. The optimal screening scenario for female heavy smokers is biennial screening from 50 to 80 years old, yielding a cost of 21.1 k€/LYG and 10.6% mortality reduction of lung cancer relative to no screening.
Evans, 2020 ¹³⁸	Our model projections show that integrating a smoking cessation intervention into a low-dose CT screening program for lung cancer could further reduce the number of lung cancer cases and save more life-years, and is likely cost-effective compared to screening alone. To optimize the benefits of lung cancer screening, health care providers should encourage smokers participating in lung cancer screening to quit smoking at each visit.
Griffin, 2020 ¹³⁹	Evidence from ENaBL suggests that LDCT screening for lung cancer may not be cost-effective, depending on the cost-effectiveness threshold used [47]. Thresholds of £20,000 to £30,000 per QALY are commonly used in the UK, and screening is estimated to be cost-effective with the higher threshold, but not with the lower. This evaluation suggests that screening would result in a reduction in lung cancer mortality, but also an increase in lung cancer diagnoses, and additional costs. One screening strategy that was investigated provided a ratio of additional costs to benefits that was at the upper limit of what would conventionally be considered cost-effective in the UK, while other screening strategies were outside the normal range of cost-effectiveness. Screening strategies with annual or biennial scans are not expected to be cost-effective regardless of the amount one is willing to pay for benefits. Early results from the NELSON trial appear to support the positive mortality benefits demonstrated by the NLST but may also show our finding to be conservative [48]. An extension of this economic evaluation—which considers multiple programme designs and adjusts for over-diagnosis bias—to include the full findings of the NELSON trial would significantly enhance the evidence base for decision-makers wishing to consider the cost-effectiveness of lung cancer screening in the UK.
Jaine, 2020 ¹⁴⁰	Currently, LDCT screening for lung cancer in New Zealand is unlikely to be cost-effective for the overall target population defined in this study and under the modelling assumptions we used. However, there is a potential case for a more targeted screened



	population based on ethnicity given our cost-effectiveness findings for Māori. This may lead to a reduction in the large ethnic inequalities in mortality in New Zealand, some of which is due to varying lung cancer rates. Lung cancer is an important disease both in New Zealand and globally, and resources need to be maintained to reduce the harm from the disease. Our results show that it is important to investigate the heterogeneity and nuances of cost-effectiveness for certain populations in New Zealand. It would be important to monitor screening test costs and any improvements in the test sensitivity and specificity, as this may sufficiently improve the cost-effectiveness for the entire target population. Although there is a potential benefit of screening (particularly for Māori), there are currently health gains to be made by implementing tobacco control interventions that improve quitting rates and reduce uptake of smoking, such as increasing tobacco taxation [42], reducing tobacco retail outlets [43], and other tobacco endgame strategies [44].
McLeod, 2020 ¹⁴¹	A national LDCT screening programme for lung cancer in NZ is likely to be cost-effective and will improve total population health. A well-planned and monitored programme can make an important contribution to reducing inequities in the burden of lung cancer for the Māori population. For these reasons, we highly recommend consideration of an LDCT screening programme in NZ.
Veronesi, 2020 ¹⁴²	To conclude, this CEA indicates that LDCT screening is associated with the low yearly cost of 2944 euro per LY gained (ICER), which is considerably lower than the ICER considered acceptable in Europe. The implication for health policy-makers is that screening can be implemented throughout Italy – and other European countries with a similar public health system to that of Italy – at relatively low cost, thereby saving the lives of many lung cancer patients.
Health Technology Assessments (HTAs)	
UK NSC, 2022b ¹¹⁶	Based on the results presented in this interim report, the use of LDCT for lung cancer screening is likely to be cost-effective compared to no screening. Nevertheless, given that the ICER for the most cost-effective strategy in this interim report is £1,529 per QALY gained, the updated natural history model component would need to lead to an order of magnitude change for the ICER to get close to the willingness to pay threshold of £20,000 per QALY, as used by organisations like NICE.
IHE, 2014 ¹¹⁸	In a constrained health care system, other services will need to be contracted or eliminated to free the approximately \$105.68 million (annual screening) in resources needed to fund its adoption for the first five years alone. Determining whether the \$105.68 million is worth the investment depends on the opportunity cost of its adoption. That is, if decision-makers were to adopt lung cancer screening with LDCT, it is imperative that they consider carefully what services would be contracted or eliminated in order to fund its adoption, and assess their associated costs and health impacts compared to lung cancer screening with LDCT.



APPENDIX 8. PATIENTS SELECTION FLOW CHART



(*) *Note on the BCR extraction:* For all patients with at least one selected lung tumour diagnosed during the period 2015-2020 at the age of 50-79 years, all lung cancers diagnosed during the period 2015-2021 are included in the database (in case they had no previous lung cancer before 2015). It total, N = 134 tumours are added to the database: n=4 with age <50y diagnosed during the incidence years 2015-2020; n=130 diagnosed during the incidence year 2021.



APPENDIX 9. LIST OF SELECTION CRITERIA

Appendix 9.1. Diagnostic nomenclature codes

Appendix 9.1.1. Multidisciplinary Team

Codes	Label in Dutch	Label in French
350372 - 350383	Eerste multidisciplinair oncologisch consult (eerste MOC), geattesteerd door de geneesheer-coördinator	Première consultation oncologique multidisciplinaire (première COM), attestée par le médecin-coordonateur
350394 - 350405	Deelname aan multidisciplinair oncologisch consult	Participation à la concertation oncologique multidisciplinaire
350416 - 350420	Deelname aan het multidisciplinair oncologisch consult door een arts die geen deel uitmaakt van de staf van ziekenhuisgeneesheren	Participation à la concertation oncologique multidisciplinaire par un médecin qui n'est pas membre de l'équipe de médecins hospitaliers
350276 - 350280	Opvolgings-multidisciplinair oncologisch consult (opvolgings-MOC), geattesteerd door de geneesheer-coördinator	Concertation oncologique multidisciplinaire de suivi (COM de suivi), attestée par le médecin-coordonateur
350291 - 350302	Bijkomend multidisciplinair oncologisch consult (bijkomende MOC) in een ander ziekenhuis dan dit van het eerste MOC, op doorverwijzing, geattesteerd door de geneesheer-coördinator	Concertation oncologique multidisciplinaire supplémentaire (COM supplémentaire) dans un hôpital autre que celui de la première COM, sur renvoi, attestée par le médecin-coordonateur
350453 - 350464	Omschrijving vanaf 01/11/2010: Bijkomend honorarium bij de verstrekking 350372-350383, 350276-350280 en 350291-350302 aanrekenbaar door de geneesheer-specialist in de medische oncologie, of houder van de bijzondere beroepstitel in de klinische hematologie of in de pediatrische hematologie en oncologie, wanneer deze het multidisciplinair oncologisch consult coördineert	Supplément d'honoraires à la prestation 350372-350383, 350276-350280 et 350291-350302, attestable par le médecin spécialiste en oncologie médicale ou porteur du titre professionnel particulier en hématologie clinique ou en hématologie et oncologie pédiatriques, lorsque celui-ci coordonne la consultation oncologique multidisciplinaire
350475 - 350486	Bijkomend honorarium bij de verstrekking 350394-350405 of 350416-350420 aanrekenbaar door de geneesheer-specialist in de medische oncologie, of houder van de bijzondere beroepstitel in de klinische hematologie of in de pediatrische hematologie en oncologie, wanneer deze het multidisciplinair oncologisch consult bijwoont	Supplément d'honoraires à la prestation 350394-350405 ou 350416-350420, attestable par le médecin spécialiste en oncologie médicale ou porteur du titre professionnel particulier en hématologie clinique ou en hématologie et oncologie pédiatriques, lorsque celui-ci assiste à la consultation oncologique multidisciplinaire



Appendix 9.1.2. Medical Imaging

Codes	Label in Dutch	Label in French
RX thorax (or RX rib cage)		
452690 - 452701	Radiografie van de thorax en de inhoud ervan, één cliché	Radiographie du thorax et de son contenu, un cliché
452712 - 452723	Radiografie van de thorax en de inhoud ervan, minimum twee clichés	Radiographie du thorax et de son contenu, minimum 2 clichés
455335 - 455346	Radiografie van het ribrooster, minimum twee clichés	Radiographie du gril costal, minimum 2 clichés
463691 - 463702	Radiografie van de thorax en de inhoud ervan, één cliché	Radiographie du thorax et de son contenu, un cliché
463713 - 463724	Radiografie van de thorax en de inhoud ervan, minimum 2 clichés	Radiographie du thorax et de son contenu, minimum 2 clichés
CT (body) – Thoracal CT codes in bold are not included in surgical hospitalisation costs.		
459550 - 459561	Computergestuurde tomografie van de thorax met of zonder contrastmiddel, met registreren en clichés, minimum 15 coupes, voor het hele onderzoek	Tomographie commandée par ordinateur, du thorax avec/ou sans moyen de contraste, avec enregistrement et clichés, 15 coupes au minimum, pour l'ensemble de l'examen
459572 - 459583	Computergestuurde tomografie van het abdomen, met of zonder contrastmiddel, met registreren en clichés, minimum 15 coupes, voor het hele onderzoek	Tomographie commandée par ordinateur, de l'abdomen, avec/ou sans moyen de contraste, avec enregistrement et clichés, 15 coupes au minimum, pour l'ensemble de l'examen
459594 - 459605	Computergestuurde tomografie van de hals en de thorax, met of zonder contrastmiddel, met registreren en clichés, minimum 30 coupes voor het hele onderzoek	Tomographie commandée par ordinateur du cou et du thorax, avec/ou sans moyen de contraste, avec enregistrement et clichés, 30 coupes au minimum, pour l'ensemble de l'examen
459616 - 459620	Computergestuurde tomografie van de thorax en het abdomen, met of zonder contrastmiddel, met registreren en clichés, minimum 30 coupes voor het hele onderzoek	Tomographie commandée par ordinateur du thorax et de l'abdomen, avec/ou sans moyen de contraste, avec enregistrement et clichés, 30 coupes au minimum, pour l'ensemble de l'examen
459631 - 459642	Computergestuurde tomografie van de hals, de thorax en het abdomen, met of zonder contrastmiddel, met registreren en clichés, minimum 30 coupes voor het hele onderzoek	Tomographie commandée par ordinateur du cou, du thorax et de l'abdomen, avec/ou sans moyen de contraste, avec enregistrement et clichés, 30 coupes au minimum, pour l'ensemble de l'examen
CT (neck)		
458813 - 458824	Computergestuurde tomografie van de hals (weke delen) met of zonder contrastmiddel, met registreren en clichés, minimum 15 coupes, voor het hele onderzoek	Tomographie commandée par ordinateur, du cou (parties molles) avec/ou sans moyen de contraste, avec enregistrement et clichés, 15 coupes au minimum, pour l'ensemble de l'examen
MRI		



459410 - 459421	NMR-onderzoek van het hoofd (schedel, hersenen, rotsbeen, hypofyse, sinussen, orbita(e) of kaakgewrichten), minstens drie sequenties, met of zonder contrast, met registratie op optische of elektromagnetische drager	Examen d'IRM du cou ou du thorax ou de l'abdomen ou du bassin, minimum 3 séquences, avec ou sans contraste, avec enregistrement sur support soit optique, soit électromagnétique
CT (brain)		
458673 - 458684	Computergestuurde tomografie van de schedel met en/of zonder contrastmiddel, met registreren en clichés, minimum 10 coupes, voor het hele onderzoek	Tomographie du crâne commandée par ordinateur, avec ou sans moyen de contraste, avec enregistrement et clichés, 10 coupes au minimum pour l'ensemble de l'examen
458732 - 458743	Computergestuurde tomografie van de rotsbeenderen en/of sella tursica met of zonder contrastmiddel, met registreren en clichés, in een opeenvolgende reeks coupes, gelijk aan of minder dan 2 mm : minimum 20 coupes	Tomographie des rochers et/ou de la selle turcique, commandée par ordinateur, avec ou sans moyen de contraste, avec enregistrement et clichés, dans une série successive de coupes égales ou inférieures à 2 mm : 20 coupes au minimum
MRI (brain)		
459395 - 459406	NMR-onderzoek van het hoofd (schedel, hersenen, rotsbeen, hypofyse, sinussen, orbita(e) of kaakgewrichten), minstens drie sequenties, met of zonder contrast, met registratie op optische of elektromagnetische drager	Examen d'IRM de la tête (crâne, encéphale, rocher, hypophyse, sinus, orbite(s) ou articulations de la mâchoire), minimum 3 séquences avec ou sans contraste, avec enregistrement soit sur support optique, soit électromagnétique
PET – CT - 442595 – 442606 was only selected in 2014-2015 as from 2016 this code is restricted to the examination of the heart.		
442595 - 442606	Functionele scintigrafische test die twee opeenvolgende tomografische onderzoeken omvat, met verwerking op computer, die ten minste twee niet-parallelle reconstructievlakken omvat, met protocol en iconografische documenten, niet cumuleerbaar met de verstrekkingen 442411 - 442422, 442455 - 442466, 442610 - 442621 en 442632 - 442643 voor het onderzoek van een zelfde functie dat met een zelfde gemerkt produkt wordt verricht	Test scintigraphique fonctionnel comportant deux examens tomographiques successifs avec traitement par ordinateur comprenant au moins deux plans non parallèles de reconstruction, avec protocole et documents iconographiques, non cumulable avec les prestations 442411 - 442422, 442455 - 442466, 442610 - 442621 et 442632 - 442643 pour l'examen d'une même fonction effectué au moyen d'un même produit marqué
442750 - 442761	Positronentomografisch onderzoek, met protocol en documenten, voor andere indicaties dan deze vermeld bij de verstrekkingen 442971-442982, 442676-442680, 442691-442702, 442713-442724 of 442735-442746	Examen tomographique à émission de positons par détection en coïncidence, avec protocole et documents, pour d'autres indications que celles mentionnées aux prestations 442971-442982, 442676-442680, 442691-442702, 442713-442724 ou 442735-442746
459874 - 459885	Computergestuurde tomografie van de hersenen met registreren en clichés, met of zonder contrastmiddel, tegelijkertijd uitgevoerd bij een PET onderzoek, voor diagnostische doeleinden	Tomographie à émission de positons par détection en coïncidence avec protocole et documents, pour l'ensemble de l'examen, pour des indications oncologiques



459896 - 459900	Computergestuurde tomografie met registreren en clichés, met of zonder contrastmiddel, tegelijkertijd uitgevoerd bij een PET onderzoek dat tenminste een opname van de halsregio tot en met het abdomen omvat, voor diagnostische doeleinden	Tomographie du cerveau commandée par ordinateur, avec ou sans moyen de contraste, avec enregistrement et clichés, effectuée simultanément avec un examen PET, à des fins diagnostiques
459911 - 459922	Computergestuurde tomografie met registreren en clichés, met of zonder contrastmiddel, tegelijkertijd uitgevoerd bij een PET onderzoek dat tenminste een opname van de thorax omvat, voor diagnostische doeleinden	Tomographie commandée par ordinateur, avec ou sans moyen de contraste, avec enregistrement et clichés, effectuée simultanément avec un examen PET qui comprend au moins un cliché de la région du cou jusqu'à l'abdomen, à des fins diagnostiques
Scintigraphy, SPECT, SPECT - CT		
442455 - 442466	Scintigrafie van het ganse lichaam (de scintillogrammen moeten ten minste betrekking hebben op het hoofd, de romp, het abdomen, de schouder- en bekkengordels)	Scintigraphie du corps entier (les scintillogrammes doivent comporter la tête, le tronc, l'abdomen, les ceintures scapulaires et pelviennes au minimum)
442514 - 442525	Tomografisch onderzoek van een streek van het lichaam tijdens een scintigrafie van het ganse lichaam, met computerverwerking, dat ten minste twee niet parallelle reconstructievlakken omvat, met protocol en iconografische documenten	Examen tomographique d'une région du corps lors d'une scintigraphie du corps entier, avec traitement par ordinateur comprenant au moins deux plans non parallèles de reconstruction, avec protocole et documents iconographiques (Single-photon emission computed tomography - SPECT)
442396 - 442400	Tomografisch onderzoek tijdens een scintigrafie, met verwerking op computer die ten minste twee niet-parallelle reconstructievlakken omvat, met protocol en iconografische documenten,	Examen tomographique lors d'une scintigraphie, avec traitement par ordinateur comprenant au moins deux plans non parallèles de reconstruction, avec protocole et documents iconographiques (Single-photon emission computed tomography - SPECT)
442411 - 442422	Scintigrafie van een orgaan, van een stelsel of van een deel van het lichaam	Scintigraphie d'un organe, d'un système ou d'une partie du corps
442610 - 442621	Functionele scintigrafische test van een orgaan of stelsel van organen, met sequentele inzameling van de gegevens, kwantitatieve analyse met telsysteem (computer) die activiteitscurven in de tijd en/of tabellen met cijfergegevens en/of parametrische beelden omvat, met protocol en iconografische documenten	Examen scintigraphique fonctionnel d'un organe ou système d'organes, avec acquisition séquentielle (dynamique) des données qui comprend au moins trois enregistrements à différents moments, avec leur analyse quantitative comprenant des courbes d'activité dans le temps et/ou des tableaux de données chiffrées, avec protocole et documents iconographiques
459351 - 459362	Computergestuurde tomografie van het bekken en/of de wervelzuil, schedel, thorax, met of zonder contrastmiddel, met beeldfusie, bij SPECT-CT onderzoek, uitgevoerd op een SPECT-CT toestel	Tomographie commandée par ordinateur du bassin et/ou de la colonne vertébrale, du crâne ou du thorax, avec ou sans moyen de contraste, avec fusion d'images, lors d'un examen SPECT-CT, réalisé au moyen d'un appareil SPECT-CT



442536 - 442540	Bijkomend honorarium voor een lokalisatie CT opname, met beeldfusie, bij een SPECT onderzoek, uitgevoerd op een SPECT-CT toestel	Supplément d'honoraires pour lenregistrement d'un CT de localisation, avec fusion d'images, lors d'un examen SPECT, réalisé au moyen d'un appareil SPECT-CT

Appendix 9.1.3. Lung fonction testing

Codes	Label in Dutch	Label in French
471251 - 471262	Volledige spirografie met bepalen van maximum adem minuten volume	Spirographie globale avec détermination du volume expiratoire maximum seconde
471273 - 471284	Spirografie met bronchodilatatieproef	Spirographie avec épreuve de bronchodilatation
471295 - 471306	Spirografie met pharmacodynamische provocatieproef al dan niet gevolgd van bronchodilatatie	Spirographie avec épreuve pharmaco-dynamique, de provocation, suivie ou non de bronchodilatation
471310 - 471321	Bepalen van het residuair volume	Détermination du volume résiduel
471354 - 471365	Metten van diffusiecapaciteit	Mesure de la capacité de diffusion
471376 - 471380	Studie van de ventilatiemechaniek	Etude de la mécanique ventilatoire
471391 - 471402	Ergospirometrie	Ergospirométrie

Appendix 9.1.4. Biopsies

Codes	Label in Dutch	Label in French
355434 - 355445	Punctie bij ascites of borstvliesontsteking	Ponction d'ascite ou de pleurésie
355456 - 355460	Punctie voor evacuatie bij ascites of borstvliesontsteking, inclusief de eventuele inspuitingen en spoelingen	Ponction évacuatrice d'ascite ou de pleurésie, y compris les injections et lavages éventuels
355633 - 355644	Pleurabiopsie met naald	Biopsie pleurale à l'aiguille
355655 - 355666	Punctiebiopsie van een longletsel onder radiologische controle	Ponction biopsique d'une lésion pulmonaire sous contrôle radiologique



Appendix 9.1.5. Endoscopies

Codes	Label in Dutch	Label in French
Bronchoscopy		
257272 - 257283	Bronchoscope met extractie van vreemde lichamen	Bronchoscope avec extraction de corps étrangers
257294 - 257305	Bronchoscope zonder afname voor biopsie en/of bronchoscope met therapeutische aspiratie	Bronchoscope sans prélèvement biopsique, et/ou bronchoscope avec aspiration thérapeutique
257316 - 257320	Bronchoscope met afname voor biopsie en/of verwijderen van tumors en/of coagulatie van letsels	Bronchoscope avec prélèvement biopsique, et/ou ablation de tumeurs, et/ou coagulation de lésions
471715 - 471726	Bronchoscope zonder afname voor biopsie	Bronchoscope sans prélèvement biopsique
471730 - 471741	Bronchoscope met afname voor biopsie, en/of verwijderen van tumors, en/of coagulatie van letsels	Bronchoscope avec prélèvement biopsique, et/ou ablation de tumeurs, et/ou coagulation de lésions
471752 - 471763	Bronchoscope met transcarinale punctie en eventuele radioscopische controle	Bronchoscope avec ponction transcarinale et contrôle radioscopique éventuel
471774 - 471785	Bronchoscope met bronchoalveolair wassen (min. 100 ml)	Bronchoscope avec lavage broncho-alvéolaire (minimum 100 ml)
471796 - 471800	Bronchoscope met extractie van vreemde lichamen of plaatsing van een prothetisch element	Bronchoscope avec extraction de corps étrangers ou mise en place d'un élément prothétique
471811 - 471822	Bronchoscope met perifere pulmonaire afnamen voor biopsie (ofwel veelvuldige afnamen, minimum 5, ofwel geleide afname in geval van perifere tumor), inclusief de eventuele radioscopische controle	Bronchoscope avec prélèvement de biopsies pulmonaires périphériques (soit prélèvements multiples minimum 5, soit prélèvement dirigé en cas de tumeur périphérique) y compris le contrôle radioscopique éventuel
Tracheoscopy		
351035 - 351046	Tracheo- en/of laryngoscopie, met of zonder afname voor biopsie	Trachéo- et/ou laryngoscopie, avec ou sans prélèvement biopsique
471612 - 471623	Tracheoscopy met verwijderen van tumors en/of coagulatie van letsels	Trachéoscopie avec ablation de tumeurs et/ou coagulation de lésions
EBUS		
471833 - 471844	Echo-endoscopie van de bronchi	Echoendoscopie bronchique
471855 - 471866	Echo-endoscopie van de bronchi met punctie van extramuraal weefsel (disposable materiaal niet inbegrepen)	Echo-endoscopie bronchique avec ponction de tissu extramural (matériel disposable non compris)
EUS		



473852 - 473863	Onderzoek van het hogere spijsverteringskanaal en de naburige organen met een echo-endoscoop	Examen du tube digestif supérieur et des organes voisins avec un échoendoscope
473874 - 473885	Een of meer afnamen van weefsel met behulp van een naald doorheen de wand van het spijsverteringskanaal, door middel van echo-endoscopie	Prélèvement(s) à l'aiguille de tissu au travers de la paroi du tube digestif, par échoendoscopie
Mediastinoscopy		
228152 - 228163	Mediastinoscopie	Médiastinoscopie
Gastrointestinale endoscopy		
472231 - 472242	Duodenum- of dunne darmbiopsie met sonde, inclusief radioscopie	Biopsie du duodénum ou de l'intestin grêle, par sonde, radioscopie comprise
472356 - 472360	Onderzoek van de oesophagus door middel van endoscopie	Examen de l'oesophage par endoscopie
472415 - 472426	Fibrogastroscoopie en/of fibrobulboscopie	Fibro-gastroscoopie et/ou fibro-bulboscopie
472555 - 472566	Oesofagoscopie met wegnemen van tumors en/of coagulatie van letsels	Oesophagoscopie avec ablation de tumeurs et/ou coagulation de lésions
472570 - 472581	Fibrogastroscoopie en/of fibrobulboscopie met wegnemen van tumors en/of coagulatie van letsels	Fibro-gastroscoopie et/ou fibro-bulboscopie avec ablation de tumeurs et/ou coagulation de lésions
473056 - 473060	Onderzoek van het hogere spijsverteringskanaal door middel van endoscopie	Examen du tube digestif supérieur par endoscopie
473793 - 473804	Wegnemen van tumors en/of coagulatie van letsels (2e en 3e duodenum)	Ablation de tumeurs et/ou coagulation de lésions (2e et 3e duodénum)



Appendix 9.1.6. Cyto-histopathology

Codes	Label in Dutch	Label in French
Cytology		
588416 - 588420	Cytologisch onderzoek naar neoplastische cellen op afnames niet gespecificeerd in de verstrekkingen 589853-589864 en 588394-588405, ongeacht het aantal preparaten, per afname	Recherche cytologique de cellules néoplasiques sur des prélèvements non précisés dans les prestations 589853-589864 et 588394-588405, quel que soit le nombre de lames, par prélèvement
Histology		
588011 - 588022	Histologisch onderzoek door inclusie en coupe, ongeacht het aantal coupes en ongeacht het aantal onderzochte organen, en met inbegrip van het eventueel macroscopisch onderzoek, van afnames die niet overeenkomen met de verstrekkingen 588232-588243, 588254-588265, 588276-588280, 588291-588302 of 587112-587123	Examen histologique par inclusion et coupe, quel que soit le nombre de coupes et quel que soit le nombre d'organes examinés, en ce compris l'examen macroscopique éventuel, des prélèvements ne correspondant pas aux prestations 588232-588243, 588254-588265, 588276-588280, 588291-588302 ou 587112-587123
588033 - 588044	Peroperatoir pathologisch-anatomisch extempore onderzoek, ongeacht het aantal afnames, volgens de vriesmethode of depmethode en ongeacht het aantal verrichte controle-onderzoeken na inclusie en coupe	Examen peropératoire extemporané quel que soit le nombre de prélèvements par la technique de congélation ou d'apposition sur lame quel que soit le nombre de contrôles effectués après inclusion et coupe
588254 - 588265	Histologisch onderzoek door inclusie en coupe, ongeacht het aantal coupes en ongeacht het aantal onderzochte organen, en met inbegrip van het eventueel macroscopisch onderzoek, van de bipten van volgende diepe organen : - lever, - nier, - nierbekken, - bijnier, - prostaat, - borst, - lymfeklier, - beenmerg, - bot, - schildklier, - speekselklier, - pleura, - long, - testikel, - peritoneum, - retroperitoneum, - mediastinum, - hersenen en ruggenmerg, - hart, - pancreas	Examen histologique par inclusion et coupe, quel que soit le nombre de coupes et quel que soit le nombre d'organes examinés, en ce compris l'examen macroscopique éventuel, pour les biopsies des organes profonds suivants : - foie, - rein, - bassinet, - surrénale, - prostate, - sein, - ganglion lymphatique, - moelle osseuse, - os, - glande thyroïde, - glande salivaire, - plèvre, - poumon, - testicule, - péritoine, - rétropéritoine, - médiastin, - cerveau et moelle épinière, - cœur, - pancreas
588276 - 588280	Histologisch onderzoek, door inclusie en coupe, ongeacht het aantal coupes en ongeacht het aantal onderzochte organen, en met inbegrip van het eventueel macroscopisch onderzoek, van volgende operatiestukken : - lymfeklierexerese, - eenzijdige lymfeklier oksel, - eenzijdige lymfeklier lies, - heekkundige longbiopsie voor niet-oncologische indicatie, - partiële of totale thymectomie, - resectie van subfasciale tumoren, - partiële hepatectomie, - cholecystectomie, - splenectomie, - mesenteriale tumorectomie, - retroperitoneale tumorectomie, - oogbol resectie, - speekselklierresectie (met uitzondering van de accessoire speekselklieren), - partiële of totale glossectomie, - thyroïdectomie, - parathyroïdectomie, - pharyngectomie, - incisionele borstbiopsie, - borsttumorectomie, - partiële cystectomie (met uitzondering van de	Examen histologique par inclusion et coupe, quel que soit le nombre de coupes et quel que soit le nombre d'organes examinés, en ce compris l'examen macroscopique éventuel des pièces opératoires suivantes : - exérèse de ganglion lymphatique, - évidement ganglionnaire axillaire unilatéral, - évidement ganglionnaire inguinal unilatéral - biopsie pulmonaire chirurgicale pour indication non-oncologique, -thymectomie partielle ou totale, - résection de tumeur sous-fasciale, - hépatectomie partielle, - cholécystectomie, - splénectomie, - tumorectomie mésentérique, - tumorectomie rétropéritonéale, - résection du globe oculaire, - résection d'une glande salivaire (à l'exception des glandes salivaires accessoires), - glossectomie partielle ou totale, - thyroïdectomie, - parathyroïdectomie, - pharyngectomie, - biopsie par



	endoscopische blaasresectie), - prostaatactomie, - epididymectomie, - orchidectomie, - partiële penis amputatie, - diepe hals tumorectomie, - partiële nefrectomie, - adnexectomie, - ovariectomie, - salpingectomie, - partiële vulvectomie, - baarmoederhals conisatie of - resectie, - bijnier resectie, - zenuwbiopsie, - spierbiopsie, - hersen-, ruggenmerg- of hypofyse- tumor resectie, - bottumor resectie, - tonsillectomie (> 18 jaar), - adenoïdectomie (> 18 jaar)"	incision du sein, - tumorectomie du sein, - cystectomie partielle (à l'exception de la résection vésicale endoscopique), - adénomectomie prostatique, - épидидymectomie, - orchidectomie, - amputation partielle du pénis, - tumorectomie profonde du cou, - néphrectomie partielle, - annexectomie, - ovariectomie, - salpingectomie, - vulvectomie partielle, - conisation ou résection du col de l'utérus, - résection de la glande surrénale, - biopsie nerveuse- biopsie musculaire, - résection d'une tumeur du cerveau, de la moelle épinière ou de l'hypophyse - résection de tumeur osseuse, - amygdaléctomie (> 18 ans), - adénoïdectomie (> 18 ans)
588291 - 588302	Histologisch onderzoek, door inclusie en coupe, ongeacht het aantal coupes en ongeacht het aantal onderzochte organen, en met inbegrip van het eventueel macroscopisch onderzoek, van volgende operatiestukken : - partiële mastectomie met okselklier(en), -totale mastectomie met of zonder okselklier(en), - partiële of totale pneumectomie voor niet-oncologische indicatie, - partiële of totale slokdarmresectie voor niet-oncologische indicatie, - bilaterale liesklieruitruiming, - lymfeklier uitruiming van twee of meerdere groepen halsklieren, - tumorectomie van de mondbodem of het verhemelte, - maxillectomie, - partiële of totale gastrectomie voor niet-oncologische indicatie, - dunne darm resectie, - partiële of totale colectomie, - pancreatectomie voor niet-oncologische indicatie, - hysterectomie voor niet-oncologische indicatie, - abdominoperineale resectie voor niet-oncologische indicatie, - totale cystectomie voor niet-oncologische indicatie, - totale penisamputatie, - totale nefrectomie, - hartresectie, - hart long blok, - totale hepatectomie, - totale pelvectomie, - totale vulvectomie - foetus van 14 tot en met 24 weken	Examen histologique par inclusion et coupe, quel que soit le nombre de coupes et quel que soit le nombre d'organes examinés, en ce compris l'examen macroscopique éventuel des pièces opératoires suivantes : - mastectomie partielle avec ganglion(s) axillaire(s), - mastectomie totale avec ou sans ganglion(s) axillaire(s), - pneumectomie partielle ou totale pour indication non-oncologique, - résection partielle ou totale de l'oesophage pour indication nononcologique, - évidement ganglionnaire inguinal bilatéral, - évidement de deux ou plusieurs groupes de ganglions du cou, - tumorectomie du plancher buccal ou du palais, - maxillectomie, - gastrectomie partielle ou totale pour indication non-oncologique, - résection de l'intestin grêle, - colectomie partielle ou totale, - pancréatectomie pour indication non-oncologique, - hystérectomie pour indication non-oncologique, - résection abdominopérinéale pour indication non-oncologique, - cystectomie totale pour indication non-oncologique, - amputation totale du pénis, - néphrectomie totale, - résection cardiaque, - bloc coeur poumon(s), - hépatectomie totale, - pelvectomie totale, - vulvectomie totale, - foetus de 14 à 24 semaines y compris
Immunohistochemistry		
588976 - 588980	Immuunhistochemisch onderzoek voor het aantonen van farmacopredictieve of prognostische biomerkers in een tumor, per antiserum, in het kader van het voorschrijven van tumor-specifieke medicatie	Examen immunohistochemique pour mise en évidence des biomarqueurs pharmaco- prédictifs ou pronostiques au niveau d'une tumeur, par antisérum, dans le cadre de la prescription d'une médication spécifique à la tumeur
Molecular biology		
588534 - 588545	Opsporen van een verworven chromosoom of genafwijking met uitzondering van een puntmutatie door middel van een moleculair biologische methode, in de diagnostische investigatiefase van een niet-lymfoïde en niet-myeloïde vaste tumor (Cumulregel 5) (Diagnoseregule 1, 13)	Dépistage d'anomalies chromosomiques ou géniques acquises à l'exception d'une mutation ponctuelle au moyen d'une méthode de biologie moléculaire, dans la phase d'investigation diagnostique d'une tumeur solide non-lymfoïde et non-myeloïde (Règle de cumul 5) (Règle diagnostique 1, 13)



588696 - 588700	Opzoeken van genetische anomalieën volgens de methoden van hybridisatie van DNA-fragmenten	Recherche d'anomalies génétiques par les méthodes d'hybridation de fragments d'A.D.N.

Appendix 9.2. Surgery nomenclature codes

Codes	Label in Dutch	Label in French
227216 - 227220	Uitgebreide totale of gedeeltelijke longexerese met klierevidement voor oncologische aandoening	Exérèse totale élargie ou partielle du poumon avec évidement ganglionnaire pour affection oncologique
227253 - 227264	Totale of gedeeltelijke longexeresis	Exérèse totale ou partielle d'un poumon
227275 - 227286	Resectie met anastomose (broncho-bronchiaal of tracheo-bronchiaal) van een stambronchus of van de trachea via thoracotomie	Résection d'une bronche souche ou de la trachée avec anastomose (broncho-bronchique ou trachéo-bronchique) par thoracotomie
227371 - 227382	Thoracotomie met poging van exeresis	Thoracotomie avec tentative d'exérèse

Appendix 9.3. Radiotherapy nomenclature codes

Codes	Label in Dutch	Label in French
444113 - 444124	Forfaitair honorarium voor een eenvoudige uitwendige bestralingsreeks van 1 tot 10 fracties voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 1	Honoraires forfaitaires pour une série d'irradiations externes simples de 1 à 10 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 1
444135 - 444146	Forfaitair honorarium voor een eenvoudige uitwendige bestralingsreeks van minstens 11 tot 35 fracties voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 2	Honoraires forfaitaires pour une série d'irradiations externes simples de 11 à 35 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 2
444150 - 444161	Forfaitair honorarium voor een complexe uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 3	Honoraires forfaitaires pour une série d'irradiations externes complexes chez un patient qui répond aux critères ou pathologie repris en catégorie 3
444172 - 444183	Forfaitair honorarium voor een complexe uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 4	Honoraires forfaitaires pour une série d'irradiations externes complexes chez un patient qui répond aux critères ou pathologie repris en catégorie 4



444194 - 444205	Forfaitair honorarium voor een uitwendige bestralingsreeks met uitsluitend elektronen voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 9	Honoraires forfaitaires pour une série d'irradiations externes exclusives par électrons chez un patient qui répond aux critères ou pathologie repris en catégorie 9
444216 - 444220	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 7	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 7
444231 - 444242	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 9	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 9
444253 - 444264	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 8	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 8
444275 - 444286	Forfaitair honorarium voor exclusieve curietherapie voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 10 (restenosepreventie)	Honoraires forfaitaires pour curiethérapie exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 10 (prévention de resténose)
444290 - 444301	Forfaitair honorarium voor curietherapie gecombineerd met uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 5	Honoraires forfaitaires pour curiethérapie combinée à une série d'irradiations externes chez un patient qui répond aux critères ou pathologie repris en catégorie 5
444312 - 444323	Forfaitair honorarium voor curietherapie gecombineerd met uitwendige bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 6	Honoraires forfaitaires pour curiethérapie combinée à une série d'irradiations externes chez un patient qui répond aux critères ou pathologie repris en catégorie 6
444334 - 444345	Forfaitair honorarium voor een conventionele behandeling (röntgentherapie 200 tot 300 KV, contacttherapie 50 KV) van 1 tot 15 fracties voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 11	Honoraires forfaitaires pour un traitement conventionnel (röntgentherapie de 200 à 300 KV, thérapie de contact de 50 KV) de 1 à 15 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 11
444356 - 444360	Forfaitair honorarium voor de voorbereidingen met simulator van een behandeling met uitwendige bestraling of curietherapie, per bestralingsreeks voor een patiënt van categorie 1, 2, 3, 4, 4bis, 5, 6, 7 of 8, eerste simulatie, behalve voor patiënten van categorie 8 met behandeling voor prostaatkanker door permanente implantatie van radioactieve jodiumzaadjes	Honoraires forfaitaires pour les préparations avec simulation d'un traitement par irradiation externe ou de curiethérapie, par série d'irradiation pour un patient de catégorie 1, 2, 3, 4, 4bis, 5, 6, 7 ou 8, la première simulation, excepté pour les patients de catégorie 8 avec un traitement pour cancer de la prostate par implantation permanente de grains d'iode radioactifs
444371 - 444382	Forfaitair honorarium voor de voorbereidingen met simulator van een behandeling met uitwendige bestraling of curietherapie, per	Honoraires forfaitaires pour les préparations avec simulation d'un traitement par irradiation externe ou de curiethérapie, par série d'irradiation pour un patient de catégorie 2, 3, 4, 4bis, 5, 6 ou 8, deuxième simulation



	bestralingsreeks voor een patiënt van categorie 2, 3, 4, 4bis, 5, 6 of 8, tweede simulatie	
444393 - 444404	Forfaitair honorarium voor de berekening van de individuele dosisverdeling van een behandeling met uitwendige bestraling of curietherapie voor patiënten van categorie 1, 2, 3, 4, 4bis, 5, 6, 7 of 8, eerste planning	Honoraires forfaitaires pour le calcul de la distribution de la dose individuelle d'un traitement par irradiation externe ou de curiethérapie chez des patients de catégorie 1, 2, 3, 4, 4bis, 5, 6, 7 ou 8, premier planning
444415 - 444426	Forfaitair honorarium voor de berekening van de individuele dosisverdeling van een behandeling met uitwendige bestraling of curietherapie voor patiënten van categorie 2, 3, 4, 4bis, 5, 6 of 8, tweede planning	Honoraires forfaitaires pour le calcul de la distribution de la dose individuelle d'un traitement par irradiation externe ou de curiethérapie chez des patients de catégorie 2, 3, 4, 4bis, 5, 6 ou 8, deuxième planning
444430 - 444441	Bijkomend honorarium bij de verstrekking 444393 - 444404 (eerste planning) voor de berekening van de individuele driedimensionele dosisverdeling voor uitwendige bestraling voor patiënten van categorie 3, 4, 4bis	Honoraires supplémentaires lors de la prestation 444393 - 444404 (premier planning) pour le calcul de la distribution tridimensionnelle de la dose individuelle pour irradiation externe chez des patients de catégorie 3, 4, 4bis
444452 - 444463	Bijkomend honorarium bij de verstrekking 444393 - 444404 (eerste planning) voor de individuele dosisberekening met gebruik van een intensiteitsmodulatieprogramma voor bestraling met multileafcollimator voor patiënten van categorie 3, 4, 4bis	Honoraires supplémentaires lors de la prestation 444393 - 444404 (premier planning) pour le calcul de la dose individuelle avec utilisation d'un programme de modulation d'intensité pour irradiation avec un collimateur multi-lames chez des patients de catégorie 3, 4, 4bis
444474 - 444485	Honorarium voor gammagrafie bij een patiënt behandeld met uitwendige bestraling van categorie 1, 2, 3 of 4, maximum 4 per bestralingsreeks	Honoraires pour gammagraphie chez un patient de catégorie 1, 2, 3 ou 4 traité par irradiation externe, maximum 4 par série d'irradiation
444496 - 444500	Honorarium voor on-line imaging bij een patiënt behandeld met uitwendige bestraling categorie 1, 2, 3, 4, 4bis, maximum 4 per bestralingsreeks	Honoraires pour imagerie portale en ligne chez un patient de catégorie 1, 2, 3, 4, 4bis traité par irradiation externe, maximum 4 par série d'irradiation
444511 - 444522	Honorarium voor in-vivo dosimetrie bij patiënten behandeld met uitwendige bestraling van categorie 1, 2, 3, 4, 4bis, maximum 4 per bestralingsreeks	Honoraires pour dosimétrie in vivo chez des patients de catégorie 1, 2, 3, 4, 4bis traités par irradiation externe, maximum 4 par série d'irradiation
444533 - 444544	Bijkomend honorarium voor bestraling met een multileafcollimator voor de patiënten van categorie 3, 4, 4bis per bestralingsreeks	Honoraires supplémentaires pour irradiation avec un collimateur multi-lames chez des patients de catégorie 3, 4, 4bis, par série d'irradiation
444555 - 444566	Bijkomend honorarium bij curietherapie voor gebruik van een automatische afterloading apparaat op afstand voor de patiënten van categorie 5, 6, 7 of 8, per bestralingsreeks	Honoraires supplémentaires pour curiethérapie avec utilisation d'un système de chargement différé avec projecteur automatique de sources chez des patients de catégorie 5, 6, 7 ou 8, par série d'irradiation
444570 - 444581	Maskers of individuele fixatiesystemen bij uitwendige bestraling voor de patiënten van categorie 1 voor de regio hoofd en hals en voor de patiënten van categorie 2, 3, 4, 4bis, per bestralingsreeks	Masques ou systèmes de fixation individuelle lors d'irradiation externe chez des patients de catégorie 1 pour localisations tête et cou et chez des patients de catégorie 2, 3, 4, 4bis, par série d'irradiation
444592 - 444603	Individuele blokken bij een behandeling met uitwendige bestraling en/of curietherapie van patiënten van categorie 1, 2, 3, 4, 5, 6, 7 of 8, per bestralingsreeks	Blocs individualisés pour traitement par irradiation externe et/ou par curiethérapie des patients de catégorie 1, 2, 3, 4, 5, 6, 7 ou 8, par série d'irradiation



444614 - 444625	Lokalisatie CT opname uitgevoerd bij de verstrekking 444356-444360 (eerste simulatie) en/of bij de verstrekking 444371-444382 (tweede simulatie)	CT de localisation effectuée lors de la prestation 444356-444360 (1re simulation) et/ou de la prestation 444371-444382 (2e simulation)
Stereotactic body radiation therapy		
444636 - 444640	Forfaitair honorarium voor een stereotactische bestralingsreeks voor een patiënt die beantwoordt aan de criteria of lijdt aan een aandoening opgenomen in categorie 4bis, primaire tumoren, uitgezonderd hersentumoren	Honoraires forfaitaires pour une série d'irradiations stéréotaxiques chez un patient qui répond aux critères repris dans la catégorie 4bis, tumeurs primaires, à l'exception de tumeurs cérébrales
444651 - 444662	Forfaitair honorarium voor een stereotactische bestralingsreeks voor een patiënt die beantwoordt aan de criteria opgenomen in categorie 4bis, oligometastasen, uitgezonderd hersenmetastasen	Honoraires forfaitaires pour une série d'irradiations stéréotaxiques chez un patient qui répond aux critères repris dans la catégorie 4bis, oligométastases, à l'exception de métastases cérébrales
444673 - 444684	Forfaitair honorarium voor een stereotactische bestralingsreeks voor een patiënt die beantwoordt aan de criteria opgenomen in categorie 4bis, maligne hersentumoren en hersenmetastasen	Honoraires forfaitaires pour une série d'irradiations stéréotaxiques chez un patient qui répond aux critères repris dans la catégorie 4bis, tumeurs cérébrales malignes et métastases cérébrales
444695 - 444706	Forfaitair honorarium voor een stereotactische bestralingsreeks voor een patiënt die beantwoordt aan de criteria opgenomen in categorie 4bis, niet maligne hersentumoren en arterioveneuze malformaties (AVM)	Honoraires forfaitaires pour une série d'irradiations stéréotaxiques chez un patient qui répond aux critères repris dans la catégorie 4bis, tumeurs cérébrales non malignes et malformations artério-veineuses (MAV)

Appendix 9.4. Palliative care nomenclature codes

Codes	Label in Dutch	Label in French
- 109701	Bezoek, in een Sp-dienst (palliatieve zorg) door de huisarts op verzoek van de patiënt of van één van zijn naastbestaanden	Visite dans un service Sp (soins palliatifs) par le médecin généraliste à la demande du patient ou d'un de ses proches
- 597763	Honorarium voor toezicht op de rechthebbende die in een Sp-dienst (palliatieve zorg) is opgenomen vanaf de eerste dag hospitalisatie in deze dienst : vanaf de eenendertigste dag tot het einde van de zesde maand per dag	Honoraires de surveillance du bénéficiaire hospitalisé dans un service Sp (soins palliatifs) à partir du premier jour d'hospitalisation dans ce service : du trente-et-unième jour jusqu'à la fin du sixième mois, par jour
- 599782	Honorarium voor toezicht op de rechthebbende die in een Sp-dienst (palliatieve zorg) is opgenomen vanaf de eerste dag hospitalisatie in deze dienst : van de 1ste tot de 30ste dag, per dag	Honoraires de surveillance du bénéficiaire hospitalisé dans un service Sp (soins palliatifs) à partir du premier jour d'hospitalisation dans ce service : du 1er au 30e jour, par jour
- 599804	Honorarium voor toezicht op de rechthebbende die in een Sp-dienst (palliatieve zorg) is opgenomen vanaf de eerste dag hospitalisatie in deze dienst : van de 1ste tot de 30ste dag, per dag	Honoraires de surveillance du bénéficiaire hospitalisé dans un service Sp (soins palliatifs) à partir du premier jour d'hospitalisation dans ce service : par un médecin accrédité, du 1er au 30e jour, par jour



	dienst : door een geaccrediteerde arts, van de 1ste tot de 30ste dag, per dag	
- 785245	Regularisaties : Palliatieve zorgen (patiënt)	Régularisations : Soins palliatifs (patient)
427011 -	Forfaitair honorarium PC, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend aan een rechthebbende : wiens fysieke afhankelijkheidstoestand beantwoordt aan de volgende criteria : - afhankelijkheid wegens het criterium zich wassen (score 4) en het criterium zich kleden (score 4), en - afhankelijk wegens het criterium transfer en verplaatsingen (score 4) en om het criterium toiletbezoek (score 4), en - afhankelijkheid wegens het criterium continentie en het criterium eten (waarvoor één van de twee criteria een score 4 heeft en het andere criterium een score van minimum 3) en die beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	Honoraires forfaitaires PC, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués au bénéficiaire : dont l'état de dépendance physique répond aux critères suivants : - dépendance pour le critère se laver (score 4) et le critère s'habiller (score 4), et - dépendance pour le critère transfert et déplacements (score 4) et le critère aller à la toilette (score 4), et - dépendance pour le critère continence et pour le critère manger (pour laquelle un des deux critères obtient un score de 4, et l'autre un score de minimum 3) et qui répond à la définition du patient palliatif reprise au § 5bis, 1°
427033 -	Forfaitair honorarium PB, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend aan een rechthebbende : wiens fysieke afhankelijkheidstoestand beantwoordt aan de volgende criteria : - afhankelijkheid wegens het criterium zich wassen en het criterium zich kleden (score 3 of 4), en - afhankelijk wegens het criterium transfer en verplaatsingen en het criterium toiletbezoek (score 3 of 4), en - afhankelijkheid wegens het criterium continentie en/of het criterium eten (score 3 of 4) en die beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	Honoraires forfaitaires PB, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués au bénéficiaire : dont l'état de dépendance physique répond aux critères suivants : - dépendance pour le critère se laver et le critère s'habiller (score 3 ou 4), et - dépendance pour le critère transfert et déplacements et le critère aller à la toilette (score 3 ou 4), et - dépendance pour le critère continence et/ou pour le critère manger (score 3 ou 4). et qui répond à la définition du patient palliatif reprise au § 5bis, 1°
427055 -	Forfaitair honorarium PA, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend : aan een rechthebbende wiens fysieke afhankelijkheidstoestand beantwoordt aan de volgende criteria : - afhankelijk wegens het criterium zich wassen en het criterium zich kleden (score 3 of 4), en - afhankelijk wegens het criterium transfer en verplaatsingen en/of het criterium toiletbezoek (score 3 of 4) op voorwaarde dat deze rechthebbende beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	Honoraires forfaitaires PA, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués : au bénéficiaire dont l'état de dépendance physique répond aux critères suivants : - dépendance pour le critère se laver et le critère s'habiller (score 3 ou 4), et - dépendance pour le critère transfert et déplacements et/ou le critère aller à la toilette (score 3 ou 4) sous la condition que le bénéficiaire répond à la définition de patient palliatif reprise au § 5bis, 1°
427070 -	Supplementair honorarium, forfait PN, genoemd, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend aan een rechthebbende : in wiens hoofd één of meer verstrekkingen bedoeld sub I of sub III van deze rubriek worden aangerekend, zonder dat het dagplafond bedoeld in § 4, 6° wordt bereikt ; en die beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	Honoraires supplémentaires, dits forfaits PN, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués au bénéficiaire : pour lequel une ou plusieurs prestations visées sous I ou sous III de la présente rubrique ont été attestées, sans que le plafond journalier visé au § 4, 6° n'ait été atteint ; et qui répond à la définition de patient palliatif reprise au § 5bis 1°



427092 -	Forfaitair honorarium PC, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend aan een rechthebbende : wiens fysieke afhankelijkheidstoestand beantwoordt aan de volgende criteria : - afhankelijkheid wegens het criterium zich wassen (score 4) en het criterium zich kleden (score 4), en - afhankelijk wegens het criterium transfer en verplaatsingen (score 4) en om het criterium toiletbezoek (score 4), en - afhankelijkheid wegens het criterium continentie en het criterium eten (waarvoor één van de twee criteria een score 4 heeft en het andere criterium een score van minimum 3) en die beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	Honoraires forfaitaires PC, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués au bénéficiaire : dont l'état de dépendance physique répond aux critères suivants : - dépendance pour le critère se laver (score 4) et le critère s'habiller (score 4), et - dépendance pour le critère transfert et déplacements (score 4) et le critère aller à la toilette (score 4), et - dépendance pour le critère continence et pour le critère manger (pour laquelle un des deux critères obtient un score de 4, et l'autre un score de minimum 3) et qui répond à la définition du patient palliatif reprise au § 5bis, 1°
427114 -	Forfaitair honorarium PB, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend aan een rechthebbende : wiens fysieke afhankelijkheidstoestand beantwoordt aan de volgende criteria : - afhankelijkheid wegens het criterium zich wassen en het criterium zich kleden (score 3 of 4), en - afhankelijk wegens het criterium transfer en verplaatsingen en het criterium toiletbezoek (score 3 of 4), en - afhankelijkheid wegens het criterium continentie en/of het criterium eten (score 3 of 4) en die beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	Honoraires forfaitaires PB, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués au bénéficiaire : dont l'état de dépendance physique répond aux critères suivants : - dépendance pour le critère se laver et le critère s'habiller (score 3 ou 4), et - dépendance pour le critère transfert et déplacements et le critère aller à la toilette (score 3 ou 4) et - dépendance pour le critère continence et/ou pour le critère manger (score 3 ou 4). et qui répond à la définition du patient palliatif reprise au § 5bis, 1°
427136 -	Forfaitair honorarium PA, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend aan een rechthebbende wiens fysieke afhankelijkheidstoestand beantwoordt aan de volgende criteria : - afhankelijk wegens het criterium zich wassen en het criterium zich kleden (score 3 of 4), en - afhankelijk wegens het criterium transfer en verplaatsingen en/of het criterium toiletbezoek (score 3 of 4) op voorwaarde dat deze rechthebbende beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	Honoraires forfaitaires PA, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués : au bénéficiaire dont l'état de dépendance physique répond aux critères suivants : - dépendance pour le critère se laver et le critère s'habiller (score 3 ou 4), et - dépendance pour le critère transfert et déplacements et/ou le critère aller à la toilette (score 3 ou 4) sous la condition que le bénéficiaire répond à la définition de patient palliatif reprise au § 5bis, 1°
427151 -	Supplementair honorarium forfait PN genoemd, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend aan een rechthebbende : in wiens hoofde één of meer verstrekkingen bedoeld sub I of sub III van deze rubriek worden aangerekend, zonder dat het dagplafond bedoeld in § 4, 6° wordt bereikt; en die beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	Honoraires supplémentaires, dits forfaits PN, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués au bénéficiaire : pour lequel une ou plusieurs prestations visées sous I ou sous III de la présente rubrique ont été attestées, sans que le plafond journalier visé au § 4, 6° n'ait été atteint; et qui répond à la définition de patient palliatif reprise au § 5bis, 1°
427173 -	Forfaitair honorarium PP, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend: aan een rechthebbende in wiens hoofde de bepalingen in § 4, 6° van toepassing zijn;	Honoraires forfaitaires PP, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués : au bénéficiaire pour qui



	op voorwaarde dat deze rechthebbende beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	s'appliquent les dispositions du § 4, 6°; sous la condition que le bénéficiaire répond à la définition de patient palliatif reprise au § 5bis, 1°
427195 -	Forfaitair honorarium PP, dat één keer per verzorgingsdag wordt toegekend voor het geheel van de verpleegkundige verzorging, verleend : aan een rechthebbende in wiens hoofde de bepalingen in § 4, 6° van toepassing zijn; op voorwaarde dat deze rechthebbende beantwoordt aan de definitie van palliatieve patiënt, zoals bedoeld in § 5bis, 1°	Honoraires forfaitaires PP, accordés une seule fois par journée de soins pour l'ensemble des soins infirmiers effectués : au bénéficiaire pour qui s'appliquent les dispositions du § 4, 6° sous la condition que le bénéficiaire répond à la définition de patient palliatif reprise au § 5bis, 1°
564211 -	Individuele kinesitherapie-zitting waarbij de persoonlijke betrokkenheid van de kinesitherapeut per rechthebbende een globale gemiddelde duur van 30 minuten heeft	Séance individuelle de kinésithérapie dans laquelle l'apport personnel du kinésithérapeute par bénéficiaire atteint une durée globale moyenne de 30 minutes
564233 -	Individuele kinesitherapie-zitting waarbij de persoonlijke betrokkenheid van de kinesitherapeut per rechthebbende een globale gemiddelde duur van 15 minuten heeft : 2de zitting van de dag	Séance individuelle de kinésithérapie dans laquelle l'apport personnel du kinésithérapeute par bénéficiaire atteint une durée globale moyenne de 15 minutes : 2ème séance de la journée
740213 -	Forfait palliatieve thuispatiënten	Forfait patients palliatifs à domicile
774056 -	Overeenkomsten met de multidisciplinaire begeleidingsequipes voor palliatieve verzorging : palliatieve verzorging, eenmalig forfaitair bedrag	Conventions avec les équipes d'accompagnement multidisciplinaires pour les soins palliatifs : soins palliatifs, montant forfaitaire unique
774071 -	Overeenkomsten met de multidisciplinaire begeleidingsequipes voor palliatieve verzorging : palliatieve verzorging, verminderd forfaitair bedrag	Conventions avec les équipes d'accompagnement multidisciplinaires pour les soins palliatifs : soins palliatifs, montant forfaitaire réduit
775530 - 775541	Overeenkomsten , overschrijding van de "normale facturatiecapaciteit" (facturatie aan een verminderde prijs), dagcentra voor palliatieve verzorging, revalidatieprogramma voor psychotici	Conventions , dépassement de la "capacité normale de facturation" (facturation d'un prix réduit), centres de jour pour soins palliatifs, programmes de rééducation fonctionnelle pour psychotiques
775611 - 775622	Overeenkomsten , overschrijding van de "normale facturatiecapaciteit" (facturatie aan een verminderde prijs), dagcentra voor palliatieve verzorging, motorische revalidatie	Conventions , dépassement de la "capacité normale de facturation" (facturation d'un prix réduit), centres de jour pour soins palliatifs, rééducation motrice
775633 - 775644	Overeenkomsten , overschrijding van de "normale facturatiecapaciteit" (facturatie aan een verminderde prijs), dagcentra voor palliatieve verzorging, psychosociale revalidatie	Conventions , dépassement de la "capacité normale de facturation" (facturation d'un prix réduit), centres de jour pour soins palliatifs, rééducation psychosociale
784092 -	Inhaalforfait voor de multidisciplinaire begeleidingsequipes voor palliatieve verzorging	Forfait de rattrapage pour les équipes d'accompagnement multidisciplinaires de soins palliatifs
- 109701	Bezoek, in een Sp-dienst (palliatieve zorg) door de huisarts op verzoek van de patiënt of van één van zijn naastbestaanden	Visite dans un service Sp (soins palliatifs) par le médecin généraliste à la demande du patient ou d'un de ses proches



- 597763	Honorarium voor toezicht op de rechthebbende die in een Sp-dienst (palliatieve zorg) is opgenomen vanaf de eerste dag hospitalisatie in deze dienst : vanaf de eenendertigste dag tot het einde van de zesde maand per dag	Honoraires de surveillance du bénéficiaire hospitalisé dans un service Sp (soins palliatifs) à partir du premier jour d'hospitalisation dans ce service : du trente-et-unième jour jusqu'à la fin du sixième mois, par jour

Appendix 9.5. Systemic therapy ATC codes

ATC code	New ATC code	Label	Type
L01AA01		Cyclophosphamide	Chemotherapy
L01AA02		Chlorambucil	Chemotherapy
L01AA03		Melphalan	Chemotherapy
L01AA06		Ifosfamide	Chemotherapy
L01AA09		Bendamustine	Chemotherapy
L01AB01		Busulfan	Chemotherapy
L01AC01		Thiotepa	Chemotherapy
L01AD01		Carmustine	Chemotherapy
L01AD02		Lomustine	Chemotherapy
L01AX03		Temozolomide	Chemotherapy
L01AX04		Dacarbazine	Chemotherapy
L01BA04		Pemetrexed	Chemotherapy
L01BB02		Mercaptopurine	Chemotherapy
L01BB03		Tioguanine	Chemotherapy
L01BB04		Cladribine	Chemotherapy
L01BB05		Fludarabine	Chemotherapy
L01BC01		Cytarabine	Chemotherapy
L01BC02		Fluorouracil	Chemotherapy
Exclusion cnk			



for topical use:

706044, 38521

L01BC05	Gemcitabine	Chemotherapy
L01BC06	Capecitabine	Chemotherapy
L01BC07	Azacitidine	Chemotherapy
L01BC08	Decitabine	Chemotherapy
L01BC59	Trifluridine, combinations	Chemotherapy
L01CA01	Vinblastine	Chemotherapy
L01CA02	Vincristine	Chemotherapy
L01CA03	Vindesine	Chemotherapy
L01CA04	Vinorelbine	Chemotherapy
L01CB01	Etoposide	Chemotherapy
L01CD01	Paclitaxel	Chemotherapy
L01CD02	Docetaxel	Chemotherapy
L01CD04	Cabazitaxel	Chemotherapy
L01CX01	Trabectedin	Chemotherapy
L01DA01	Dactinomycin	Chemotherapy
L01DB01	Doxorubicin	Chemotherapy
L01DB02	Daunorubicin	Chemotherapy
L01DB03	Epirubicin	Chemotherapy
L01DB07	Mitoxantrone	Chemotherapy
L01DC01	Bleomycin	Chemotherapy
L01DC03	Mitomycin	Chemotherapy
L01EB02	Erlotinib	Targeted therapy
L01ED05	Lorlatinib	Targeted therapy
L01EL01	Ibrutinib	Targeted therapy



L01FC01		Daratumumab	Targeted therapy
L01FF06		Cemiplimab	Immunotherapy
L01FG01		Bevacizumab	Targeted therapy
L01XA01		Cisplatin	Chemotherapy
L01XA02		Carboplatin	Chemotherapy
L01XA03		Oxaliplatin	Chemotherapy
L01XB01		Procarbazine	Chemotherapy
L01XC02	L01FA01 (from 2022)	Rituximab	Targeted therapy
L01XC03	L01FD01 (from 2022)	Trastuzumab	Targeted therapy
L01XC05	L01FX02 (from 2022)	Gemtuzumab ozogamicin	Targeted therapy
L01XC06	L01FE01 (from 2022)	Cetuximab	Targeted therapy
L01XC07	L01FG01 (from 2022)	Bevacizumab	Targeted therapy
L01XC08	L01FE02 (from 2022)	Panitumumab	Targeted therapy
L01XC11	L01FX04 (from 2022)	Ipilimumab	Immunotherapy
L01XC12	L01FX05 (from 2022)	Brentuximab vedotin	Targeted therapy
L01XC13	L01FD02 (from 2022)	Pertuzumab	Targeted therapy
L01XC14	L01FD03 (from 2022)	Trastuzumab emtansine	Targeted therapy
L01XC15	L01FA03 (from 2022)	Obinutuzumab	Targeted therapy
L01XC17	L01FF01 (from 2022)	Nivolumab	Immunotherapy
L01XC18	L01FF02 (from 2022)	Pembrolizumab	Immunotherapy
L01XC21	L01FG02 (from 2022)	Ramucirumab	Targeted therapy
L01XC24	L01FC01 (from 2022)	Daratumumab	Targeted therapy
L01XC27	L01FX10 (from 2022)	Olaratumab	Targeted therapy
L01XC28	L01FF03 (from 2022)	Durvalumab	Immunotherapy
L01XC31	L01FF04 (from 2022)	Avelumab	Immunotherapy
L01XC32	L01FF05 (from 2022)	Atezolizumab	Immunotherapy



L01XD04		Aminolevulinic acid	Chemotherapy
L01XE01	L01EA01 (from 2021)	Imatinib	Targeted therapy
L01XE02	L01EB01 (from 2021)	Gefitinib	Targeted therapy
L01XE03	L01EB02 (from 2021)	Erlotinib	Targeted therapy
L01XE04	L01EX01 (from 2021)	Sunitinib	Targeted therapy
L01XE05	L01EX02 (from 2021)	Sorafenib	Targeted therapy
L01XE06	L01EA02 (from 2021)	Dasatinib	Targeted therapy
L01XE07	L01EH01 (from 2021)	Lapatinib	Targeted therapy
L01XE08	L01EA03 (from 2021)	Nilotinib	Targeted therapy
L01XE10	L01EG02 (from 2021)	Everolimus	Targeted therapy
L01XE11	L01EX03 (from 2021)	Pazopanib	Targeted therapy
L01XE13	L01EB03 (from 2021)	Afatinib	Targeted therapy
L01XE14	L01EA04 (from 2021)	Bosutinib	Targeted therapy
L01XE15	L01EC01 (from 2021)	Vemurafenib	Targeted therapy
L01XE16	L01ED01 (from 2021)	Crizotinib	Targeted therapy
L01XE17	L01EK01 (from 2021)	Axitinib	Targeted therapy
L01XE18	L01EJ01 (from 2021)	Ruxolitinib	Targeted therapy
L01XE21	L01EX05 (from 2021)	Regorafenib	Targeted therapy
L01XE23	L01EC02 (from 2021)	Dabrafenib	Targeted therapy
L01XE24	L01EA05 (from 2021)	Ponatinib	Targeted therapy
L01XE25	L01EE01 (from 2021)	Trametinib	Targeted therapy
L01XE26	L01EX07 (from 2021)	Cabozantinib	Targeted therapy
L01XE27	L01EL01 (from 2021)	Ibrutinib	Targeted therapy
L01XE28	L01ED02 (from 2021)	Ceritinib	Targeted therapy
L01XE29	L01EX08 (from 2021)	Lenvatinib	Targeted therapy
L01XE31	L01EX09 (from 2021)	Nintedanib	Targeted therapy



L01XE33	L01EF01 (from 2021)	Palbociclib	Targeted therapy
L01XE35	L01EB04 (from 2021)	Osimertinib	Targeted therapy
L01XE36	L01ED03 (from 2021)	Alectinib	Targeted therapy
L01XE39	L01EX10 (from 2021)	Midostaurin	Targeted therapy
L01XE42	L01EF02 (from 2021)	Ribociclib	Targeted therapy
L01XE50	L01EF03 (from 2021)	Abemaciclib	Targeted therapy
L01XX01		Amsacrine	Chemotherapy
L01XX05		Hydroxycarbamide	Chemotherapy
L01XX11		Estramustine	Chemotherapy
L01XX14	L01XF01 (from 2021)	Tretinoin	Chemotherapy
L01XX17	L01CE01 (from 2021)	Topotecan	Chemotherapy
L01XX19	L01CE02 (from 2021)	Irinotecan	Chemotherapy
L01XX23		Mitotane	Chemotherapy
L01XX32	L01XG01 (from 2021)	Bortezomib	Targeted therapy
L01XX35		Anagrelide	Chemotherapy
L01XX41		Eribulin	Chemotherapy
L01XX43	L01XJ01 (from 2021)	Vismodegib	Targeted therapy
L01XX44		Aflibercept	Targeted therapy
L01XX45	L01XG02 (from 2021)	Carfilzomib	Targeted therapy
L01XX50	L01XG03 (from 2021)	Ixazomib	Targeted therapy
L01XX52		Venetoclax	Targeted therapy

The second column contains the ATC alterations that took between 2005 and 2024 (source: [WHOCC - ATC alterations](#)), as the IMA uses an ATC conversion table CNK - ATC codes which is more recent than the data delivered to the BCR.



APPENDIX 10. IMA – BCR DATA TRANSMISSION

Appendix 10.1. Nomenclature codes

Chapter	Inclusion (except a or b)	(a) Inclusion on request	(b) Exclusion
II – Consultations, visits and advices, psychotherapy and other services	NO	109701 GP visit in a palliative Sp ward (included ni the present report)	
III – Routine care	Section 1. Technical interventions Palliative care in section 4		Section 2. Dentistry Section 3. Physiotherapy Section 4. Nursing care other than palliative care
IV - Deliveries	NO		YES
V – Special medical techniques	YES : special techniques, anesthesiology, surgery, medical imaging, radio- en radiumtherapy, internal medicine, dermatology,surveillance)	Tumour markers dosage (section 11)	Section 4 Reanimation Section 10 Physiotherapy and revalidation (physicians) Section 11 Clinical biology Section 13: supplementary fees (night, weekends, ...)
VI – Spectacles, hearing aids, bandages orthopaedic devices and other prostheses	Post-mammectomy material, trachea cannula, incontinence material and ostomy material	Exceptions to be requested.	YES
VII - Anatomopathology and genetic testing	YES		NO
VIII – Medical imaging-guided percutaneous interventions	YES		NO
IX - Implants		Exceptions to be requested.	YES
X – Speech therapy	NO		YES



Appendix 10.2. ATC codes not available in BCR – IMA – AIM data.

ATC code	Label
A01AA	Caries prophylactic agents
A08	Antiobesity preparations, excl. diet products
A13	Tonics
A15	Appetite stimulants
A16	Other alimentary tract and metabolism products
B06	Other hematological agents
D10	Anti-acne preparations
D11	Other dermatological preparations
J04B	Drugs for treatment of lepra
J06A	Immune sera
J07	Vaccins (except J07BM papillomavirus vaccins)
M01C	Specific antirheumatic agents
M02	Topical products for joint and muscular pain
M03	Muscle relaxants
M09	Other drugs for disorders of the musculo-skeletal system
P	Antiparasitic products, insecticides and repellents
R01	Nasal preparations
R06	Antihistamines for systemic use
R07	Other respiratory system products
S01F	Mydriatics and cycloplegics
S01G	Decongestants and antiallergics
S01L	Ocular vascular disorder agents
V01	Allergens
V03AB	Antidots
V03AC	Iron chelating agents



V03AZ	Nerve depressants
V20	Surgical dressings



APPENDIX 11. SEARCH STRATEGY – WEBSITES HTA INSTITUTES

In October 2023, the same websites of the INAHTA members visited for economic evaluation (see Table 94) were also consulted in order to find evaluations on ethical considerations of lung cancer screening or methodological guidelines on ethical HTA evaluation.

Table 117 provide an overview of the 7 HTA reports selected because an ethical dimensions of lung cancer screening were mentioned and the final decision of keeping them or not (incl. the reason for exclusion).

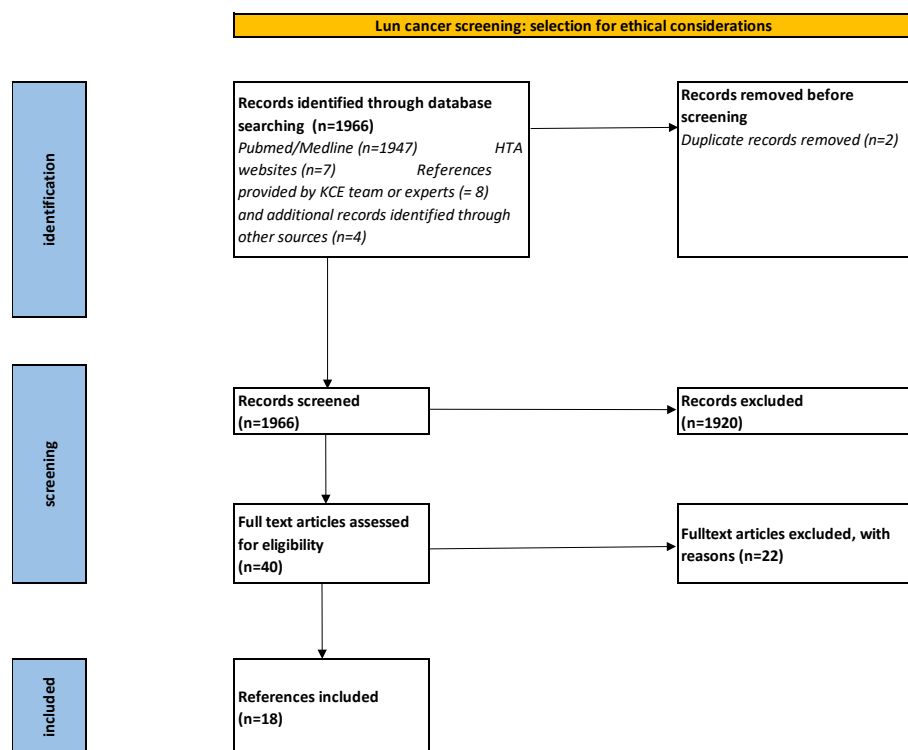
Table 117 – List of identified HTA reports with an ethical dimension

References	Final decision (reason(s) for exclusion)
Identified HTA reports with ethical mentions	
Swedish Council on Technology Assessment in Health Care (SBU). Computed tomography in screening for lung cancer. December 2002.	Excluded (existence of more recent HTA report with the same ethical issues raised)
Haute Autorité de Santé (HAS). Methodological guide. Assessment of ethical aspects. April 2013	Included
Haute Autorité de Santé (HAS). Cancer du poumon: évaluation de la pertinence d'un dépistage des populations fortement exposées au tabac en France. Note de cadrage. Septembre 2014.	Excluded (existence of more recent HAS report on the same topic)
Haute Autorité de Santé (HAS). Pertinence du dépistage du cancer broncho-pulmonaire en France. Point de situation sur les données disponibles. Analyse critique des études contrôlées randomisées. Rapport d'orientation. Janvier 2016.	Excluded (existence of more recent HAS report on the same topic)
Haute Autorité de Santé (HAS). Dépistage du cancer bronchopulmonaire par scanner thoracique faible dose sans injection: Actualisation de l'avis de 2016. Rapport d'orientation. Décembre 2021.	Included
UK National Screening Committee (NSC). Targeted screening for lung cancer in individuals at increased risk. September 2022. Targeted Lung Cancer Screening – Stakeholders Consultation Responses	Excluded (not a report but a stakeholder review of UK NSC report. Some interesting ethical issues also retrieved in the selected scientific references or identified during the stakeholders meeting)
Switzerland. Basel institute for clinical epidemiology and biostatistics. Low-dose CT screening for lung cancer. June 2022	Included



APPENDIX 12. PROCESS OF IDENTIFICATION AND SELECTION OF THE REFERENCES – ETHICAL LITERATURE

Figure 43 – Selection of relevant references for ethical considerations in lung cancer screening (flow chart)





■ REFERENCES

1. Belgian Cancer Registry. Cancer Fact Sheets, Incidence Year 2021. Brussels: 2023.
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4. Gisle L, Demarest S, Drieskens S. Gezondheidsenquête 2018: Gebruik van tabak. Brussel: 2019. (D/2019/14.440/57) Available from: https://www.sciensano.be/sites/default/files/ta_rapport2_his2018_nl_v3.pdf
5. Gerkens S, Merkur S. Belgium: Health System Review. Health Syst Transit. 2020;22(5):1-237.
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