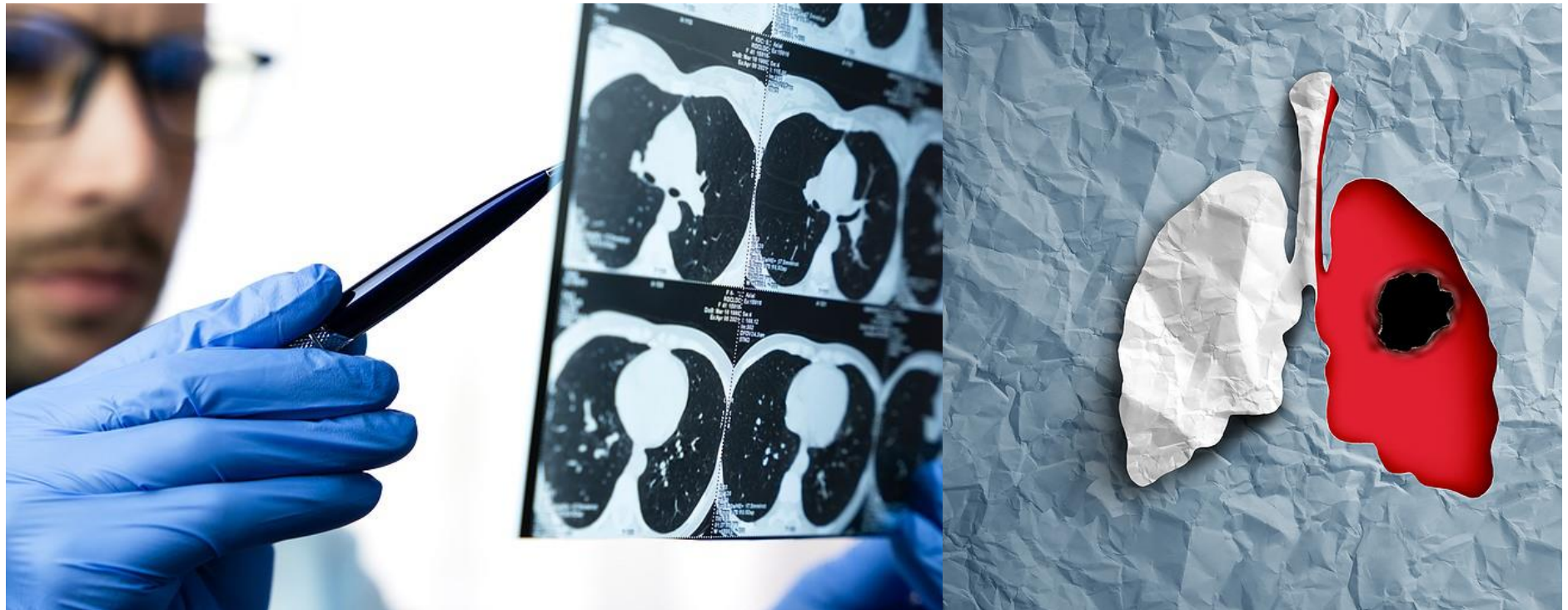


SYNTHESIS

LUNG CANCER SCREENING IN A HIGH-RISK POPULATION



SYNTHESIS

LUNG CANCER SCREENING IN A HIGH-RISK POPULATION

FABIAN DESIMPEL, JANIS LUYTEN, CÉCILE CAMBERLIN, CÉLIA PRIMUS-DE JONG, LEEN VERLEYE, MATTIAS NEYT



■ FOREWORD

Lung cancer is common, but unfortunately it is currently usually detected at a late stage. The chances of cure are then very limited. Consequently, in recent Belgian cancer mortality statistics, lung cancer is at the top. Would it perhaps be a solution to screen high-risk individuals, e.g. (former) smokers, to identify the disease at an early stage? After all, treatment options and prognosis are significantly better at an early stage. Low-dose CT scan (LDCT) could be used for such systematic screening, at least if it proved effective and cost-effective. The KCE was asked exactly this question.

An effective screening programme can save lives, but there are always downsides. These may include unclear results that require further medical tests, false-positive results where a person falsely fears he/she is suffering from cancer or even undergoes unnecessary surgery, and so on. A fast-growing cancer may also be detected between screening rounds, while other cancers that were detected at screening might never have led to problems. In short, it is important to weigh the pros and cons carefully. This is what KCE did, by evaluating the literature, and then creating its own model for calculating cost-effectiveness in Belgium.

In neighbouring countries, there are many voices advocating lung cancer screening with LDCT, and in some countries the introduction of systematic population screening is already being prepared. As you will read, the picture for Belgium outlined in the KCE report is more nuanced. Indeed, the KCE model tries to include as many cost and clinical factors involved in lung cancer screening as possible, and therefore includes more parameters than many other models. It also relies as much as possible on real data rather than assumptions. The basis of the model is visually summarised in a figure showing the impact of screening on 1,000 high-risk individuals, indicating that there is a delicate balance between clinical benefits and harms. It is now up to policymakers to make a careful decision based on this data, cost-effectiveness, and any additional organisational, ethical and budgetary considerations.

Finally, should it be decided to introduce systematic lung cancer screening for high-risk individuals, the visual representation in this report of the various benefits and harms can also be enlightening for potential future participants. After all, it is important to inform them correctly so that they can make an informed decision on whether they wish to participate, or not.

Christophe JANSSENS
Deputy Managing Director

Marijke EYSEN
Managing director a.i.(until 29 February
2024)

Ann VAN DEN BRUEL
Managing Director



■ KEY MESSAGES

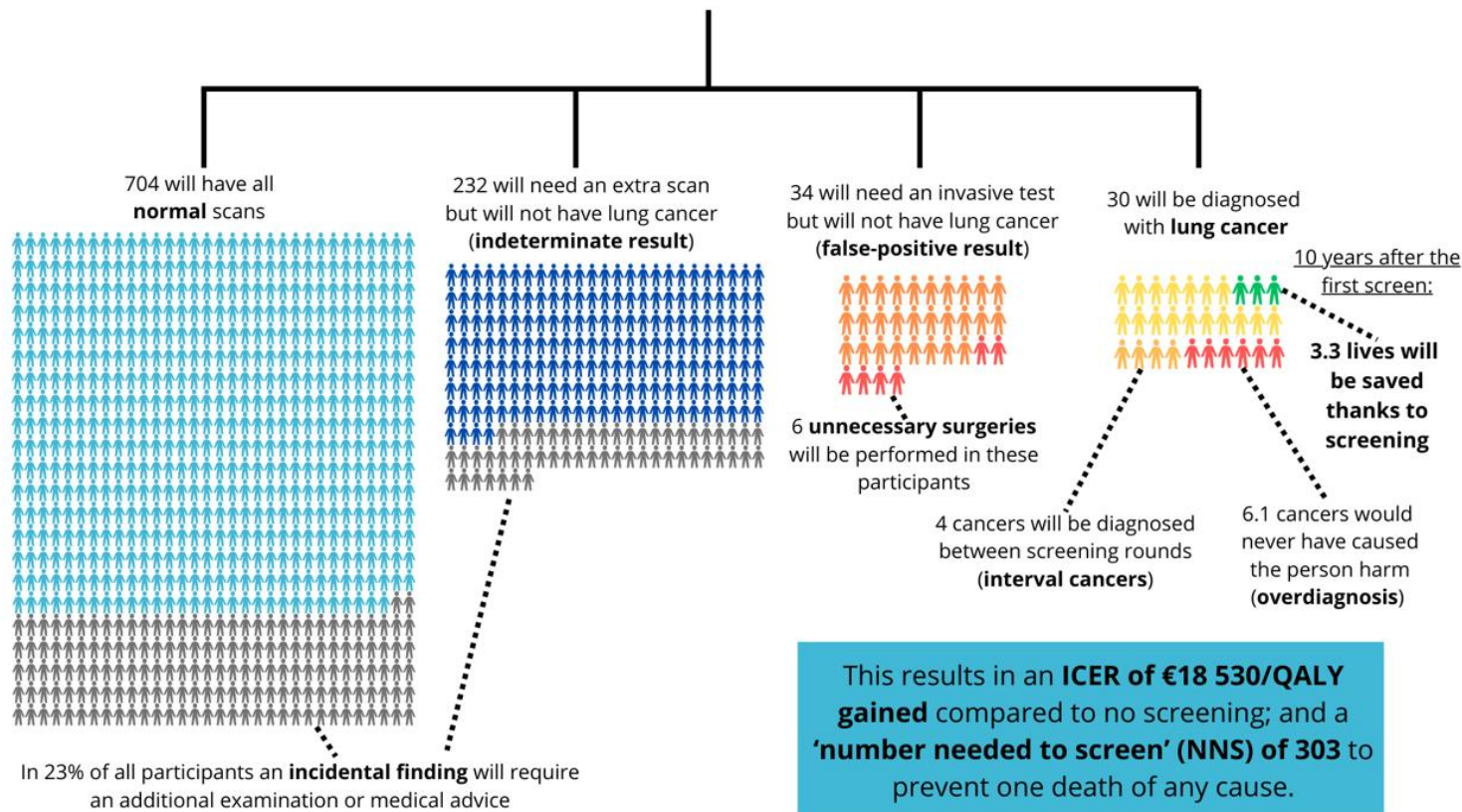
- Lung cancer is often diagnosed at an advanced stage. **Low-dose CT screening of (former) smokers** at high risk of lung cancer is a strategy to detect the disease at an early stage. In this way, treatment is less invasive and deaths are reduced.
- Before a screening programme is organised by the government, a **thorough assessment of its effectiveness, safety and cost-effectiveness** is essential. KCE was asked to conduct this evaluation.
- The KCE conducted systematic literature reviews and relied on Belgian data. It organised meetings with doctors involved in lung cancer care, screening experts and patient associations.
- The result of this study shows that lung cancer screening is associated with **significant benefits and harms**, which are summarised in the figure below.
- Lung cancer screening has been shown to reduce **lung cancer mortality** and **overall mortality** among the screened high-risk individuals.
- On the other hand, some participants receive an **indeterminate result** where a new scan is performed. There is also sometimes a **false-positive result**. That 'false alarm' is then revealed by additional, invasive investigations such as biopsies, bronchoscopies, or even surgical procedures. Apart from the unnecessary stress this causes, these procedures can also sometimes cause complications.
- In some participants, tumours are treated that would not have evolved or would have evolved very slowly without screening and that would not have posed a danger because the screened person would have died earlier from another disease or from old age (**overdiagnosis and overtreatment**).
- **Incidental findings** are frequent as a scan of the entire chest is performed. These often trigger additional investigations, and it is currently unclear whether this leads to a positive or negative impact at a population level.
- In the long term, there is also a limited **risk of cancer from radiation exposure** due to repeatedly performing an LDCT.
- **These benefits and harms are significant.** It is therefore important for the government to weigh them up carefully when considering lung cancer screening. And if it decides to launch screening, potential participants should also be given full and clear information about it beforehand. This is an ethical obligation, even if it leads to lower participation rates.



- Our cost-effectiveness analysis shows that lung cancer screening in Belgium would result in an incremental cost of €77 747/100 participants and 4.64 QALYs gained/100 participants. This amounts to an **ICER of €18 530/QALY gained compared to no lung cancer screening**.
- Lung cancer screening can be cost-effective if **the government's willingness to pay** is between €20 000 and €30 000 per QALY gained.
- A number of **variables** have a significant impact on the ICER, such as the number of overdiagnoses, price discounts on cancer therapies, the cost of reaching and inviting the target group and the number of participants.
- After this assessment of the effectiveness, safety and cost-effectiveness of a possible population screening, other factors such as **the impact on the health budget and the healthcare system** should also be taken into account in the next phase. This was not part of the scope of the current KCE study, but it can serve as a basis for identifying this impact.



LDCT screening has potential benefits and harms. When screening 1000 high-risk individuals 3 times, we estimate that:



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 biopsy or bronchoscopy. The information to form mutually exclusive groups after three rounds of screening is from Horeweg et al.² Information on the number of surgeries for false positives is from van 't Westeinde et al.³

Note: The 1000-person figure is also available for other scenarios of overdiagnosis in our scientific report.



■ SYNTHESIS

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LIST OF ABBREVIATIONS

ABBREVIATIONS

BCR

CEA

COPD

CT

FANC

HPV

HTA

ICER

IMA

LDCT

LYG

NELSON

NNS

NLST

NSCLC

QALY

NIHDI

SCLC

WHO

DEFINITION

Belgian Cancer Registry

Cost-effectiveness analysis

Chronic obstructive pulmonary disease

Computed tomography

Federal Agency for Nuclear Control

Human papillomavirus

Health Technology Assessment

Incremental cost-effectiveness ratio

Intermutualistic agency

Low-dose computed tomography

Life-years gained

Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON)

Number needed to screen

US National Lung Screening Trial

Non-small cell lung carcinoma

Quality-adjusted life-year

National Institute for Health and Disability Insurance

Small cell lung carcinoma

World Health Organization



1. INTRODUCTION

1.1. Why lung cancer screening?

Lung cancer is one of the most common cancers and the leading cause of cancer mortality in Belgium. The chance of survival depends mainly on the stage of the disease at the start of treatment. The earlier the disease is detected, the higher the chance of survival.

Since early-stage lung cancer often presents no symptoms, the disease is often diagnosed at an advanced stage leading to limited treatment options and poor prognosis. Low-dose CT screening (LDCT, see Box 1) of high-risk individuals (including (former) smokers) is a strategy to detect lung cancer at an early stage and reduce mortality (WHO fact sheet).¹ Large studies on this have already been conducted worldwide, including the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), the results of which were published in 2020.⁴

Box 1 – What is a low-dose CT scan?

Low-dose CT^a, abbreviated LDCT, is a medical imaging technique that creates detailed cross sections of the body using radioactive beams (X-rays).

An LDCT uses a lower dose of radiation than a standard CT scan. As a result, the patient is exposed to less harmful radiation, while image quality remains high enough to detect a tumour. In lung cancer screening, an LDCT of the chest is taken.

According to Sciensano's most recent Health Survey (2018)^b, about one in five Belgians aged 15 and over smoke.⁵ Lung cancer screening can be an important addition in the fight against lung cancer, but **the best preventive and most cost-effective measures are, never start smoking or stop smoking**.⁶ In Belgium, the federal states are responsible for health promotion and disease prevention.⁷ They currently support smoking cessation by partially reimbursing counselling with recognised tobacologists.⁸⁻¹⁰

1.2. No lung cancer screening in our country yet

A screening can be opportunistic or systematic, but is always done in persons without symptoms. An opportunistic screening is done following the doctor's suggestion to the patient or at the patient's request to the doctor. It is often done in the context of a consultation for another reason. For example, the doctor may suggest to a patient of 50 who comes for a consultation for a blood pressure measurement to be screened for breast cancer.

In systematic or population screening, part of the population receives an invitation for a particular examination. Currently, systematic cancer screening already exists in (some parts of) Belgium for:

- cervical cancer;
- breast cancer;
- colorectal cancer.

For lung cancer, population screening is not yet organised in our country. It is essential to realise that each screening has specific advantages and disadvantages that should be carefully weighed when considering a screening programme.

^a CT is the abbreviation for computed tomography

^b <https://www.sciensano.be/nl/projecten/gezondheidsenquête-0>



This was also stated by the European Council, which on 9 December 2022 "invited Member States to consider lung cancer screening, taking into account the burden of disease and available healthcare resources, the risk-benefit ratio, the cost-effectiveness of cancer screening, and experience from clinical trials and pilot projects."¹¹

European studies are currently investigating how best to organise a population-based lung cancer screening programme. These include looking at the most optimal and cost-effective strategy for reaching and inviting eligible individuals, and how smoking cessation programmes can be integrated into a screening programme.

A Flemish multidisciplinary working group including pulmonologists, radiologists, thoracic surgeons and radiotherapists asked the KCE to assess the cost-effectiveness of systematic lung cancer screening in high-risk individuals in Belgium.

1.3. What have we researched?

In this *Health Technology Assessment* (HTA, see Box 2), we seek to answer the following research questions:

1. What is the safety and effectiveness of lung cancer screening with LDCT in individuals at high risk of lung cancer? What are the potential benefits (prevention of death and positive impact on quality of life) and drawbacks (overdiagnosis, false-positive and false-negative results, ...)?
2. What is the cost-effectiveness of possible Belgian lung cancer screening with LDCT in individuals at high risk of lung cancer?
3. What ethical questions should be considered in lung cancer screening?

Box 2 – What is a Health Technology Assessment?

Health Technology Assessments (HTA) examine the effectiveness and safety of a medical technology (drug, implant, vaccine, screening or surgical technique...). They then assess whether the technology is cost-effective. This involves assessing the ratio between the additional cost of introducing the technology compared to the current situation and the benefit it provides to the patient and society in terms of number of life years gained and quality of life.

Besides these medical and economic elements, an HTA can also take into account organisational, social, legal and ethical aspects.

Initially, we were also going to examine what impact this screening would have on the healthcare budget. We were ultimately unable to conduct this analysis due to time constraints. Already on the basis of our information on safety/efficacy and cost-effectiveness of lung cancer screening, policymakers can decide whether they wish to organise lung cancer screening. In that case, a budget impact analysis can be carried out, based on elements presented in this study.

Were also not investigated in the current study: screening for lung cancer in non-smokers and the impact of any screening on the healthcare system (e.g. increased workload, reduced availability of CT scans for other investigations, etc.).



1.4. How did we proceed?

This HTA was conducted according to the procedures of the [KCE Process Book](#).¹²

To answer the research questions, we used the following methods:

- A systematic literature review of the safety and clinical effectiveness of lung cancer screening with LDCT in individuals at high risk of lung cancer (Chapter 4);
- A systematic literature review of the cost-effectiveness of lung cancer screening with LDCT in individuals at high risk of lung cancer (Chapter 5);
- A Belgian cost-effectiveness analysis of lung cancer screening with LDCT compared to no screening (i.e. the current Belgian situation) (Chapter 6). For this, we relied on the NELSON study and on Belgian data on survival and costs of lung cancer obtained from the Belgian Cancer Registry (BCR) and the Intermutualistic Agency (IMA), further supplemented by information on, among other things, the impact of lung cancer on quality of life;
- A literature review on ethical aspects in lung cancer screening (Chapter 7);
- Two expert meetings and communication with doctors involved in lung cancer care (e.g. lung specialist, radiologist, radiotherapist, general practitioner), with experts involved in Belgian cancer screening programmes, and with patient representatives (see colophon).

More information on the research methods used can be found in each chapter of the scientific report.

But first, we give the reader background information on lung cancer in Belgium (Chapter 2) and briefly describe the general principles of cancer screening (Chapter 3). In Chapter 8, we discuss some elements beyond the scope of our study. Finally, in Chapter 9 you will find a brief discussion of the main findings followed by policy recommendations.



2. LUNG CANCER IN BELGIUM

2.1. Number of cases

According to the Belgian Cancer Registry (BCR), 9192 cases of lung cancer were diagnosed in our country in 2021: 5675 (62%) in men and 3517 (38%) in women.¹³ Lung cancer is the second most common cancer in both men (after prostate cancer) and women (after breast cancer) in our country. Between 2006 and 2020, its incidence increased 84% in women, while it decreased 19% in men. The incidence increases from 45-49 years and decreases from around 70-75 years.¹³

Non-small cell lung cancer (NSCLC)^c is the most common type of lung cancer in Belgium, accounting for 3 out of 4 primary lung cancers. Small-cell lung cancer (SCLC)^d accounts for about 15% of cases,¹⁴ the rest are rarer lung cancers.

2.2. Mortality from lung cancer

In 2019, 5849 patients died of lung cancer in Belgium, making it the leading cause of cancer deaths in men, and the second in women, after breast cancer. Between 2017 and 2021, 23.6% of men and 32.1% of women were still alive 5 years after diagnosis.

2.3. Staging

Diagnosis involves determining the stage of a tumour. The stage indicates where in the lungs the tumour is located, the size of the tumour, whether lymph nodes are involved and to what extent the disease has spread in the body (see Box 3). In addition, a small particle of the tumour is often removed by biopsy, and examined (tissue examination or histology) to determine the type of lung cancer.

The stage of the lung tumour is a good predictor of the likelihood of survival. On average, almost 80% of patients with stage I NSCLC were alive after 3 years (2014 to 2017), while only 15% of those with stage IV NSCLC were alive after 3 years.¹⁵ As already mentioned, lung cancer is often detected at an advanced stage: in 2021, about half of lung cancer patients in Belgium already had the disease at the most advanced stage (stage IV) at diagnosis^e.

Box 3 - Simplified representation of the different stages of lung cancer

Stage I: There is a small tumour in the lung

Stage II: The tumour in the lung is slightly larger. There may be cancer cells in the lymph nodes of the lungs

Stage III: In addition to a tumour in the lung, there are usually metastases in the lymph nodes of the mediastinum (the space between the lungs).

Stage IV: There is a tumour in the lung and there are metastases in the lung and/or other organs. This is called metastatic lung cancer.

Source : <https://www.kanker.nl/kankersoorten/longkanker/diagnose/het-stadium-van-longkanker>

2.4. Risk factors for lung cancer

A number of factors increase the risk of lung cancer. Active and passive smoking is the leading cause of lung cancer, estimated to affect 90% of men worldwide and more than 80% of women with lung cancer.¹⁶ Other causes of lung cancer include exposure to environmental factors such as air pollution, asbestos, radiation and heavy metals, and lung diseases such as tuberculosis, emphysema and chronic obstructive pulmonary disease (COPD) (see Figure 1).¹⁷

^c Non-Small Cell Lung Carcinoma

^d Small cell lung carcinoma

^e According to the BCR, 2021 data

Figure 1 – The main risk factors of lung cancer



Source: European Society for Medical Oncology (ESMO), 2019¹⁸

According to Sciensano's most recent Health Survey (2018), 19.4% of Belgians aged 15 years or older were active smokers. One fourth of these (4.7%) were heavy smokers, meaning they smoked at least 20 cigarettes a day.⁵ The number of smokers is decreasing in our country, as in 2001, 28.5% of this age group still smoked.

Many lung cancer screening programmes target individuals who have smoked or have smoked for a long time. Another approach to determining whether someone is best screened is to use multivariable models that estimate lung cancer risk. Several of these models include, in addition to smoking, risk factors such as a family history of lung cancer, asbestos exposure and COPD.¹⁹

3. GENERAL PRINCIPLES OF CANCER SCREENING

3.1. Weighing advantages against disadvantages

Systematic cancer screening aims to detect a malignant tumour in persons without symptoms at an early or preliminary stage, so that the disease can be treated and the chances of survival improve. Because of earlier detection, treatment is usually less invasive, which also has a less negative impact on the patient's quality of life.

However, there are also disadvantages and risks associated with screening, both for the person screened and for society (see below). Before a government decides to organise population screening, it should therefore weigh them up carefully. Citizens should also be clearly informed about this beforehand, at the time of the invitation.

The original screening principles that a screening programme should meet, defined by Wilson and Jungner in 1968, were recently updated by Dobrow et al. resulting in 12 principles.²⁰

Some relate to the characteristics of the disease and the screening test used. The disease being screened for must have been present for quite some time before symptoms appear. Thus, there should still be sufficient time to detect and treat the disease and significantly improve the prognosis, versus when treatment is only started when symptoms appear. The screening test, e.g., must be sufficiently reliable and acceptable to participants.

Other principles deal with the organisational, health-economic and ethical aspects of screening. A screening programme should be cost-effective and feasible. It should also not have a negative impact on the healthcare system, e.g. not cause delays in screening people who do have symptoms.²¹ Each step in the screening process should be carefully organised, with attention to quality assurance and follow-up. Also, the outcomes by which the government assesses a screening programme retrospectively should be



well chosen. The advantages of a screening programme should clearly outweigh the disadvantages.

More information on the screening principles by Dobrow et al. can be found in Table 1 of the scientific report.

3.2. Beneficial or adverse impact of test results

3.2.1. True-positive and true-negative results

A screening can basically produce two results. If the **result** is **positive**, indications of a possible cancer have been detected. If the screening does not detect any signs, the test is **negative** (See Figure 2).

In a well-organised screening programme, in participants who have the disease but have no symptoms (yet), screening detects the disease (**true-positive**). As a result, their treatment is started in time and survival rates improve. In many cases, treatment is also less invasive and causes less discomfort. As a result, the patient has a better quality of life, than if the tumour had been detected at a later stage, after the onset of symptoms. These people benefit from the screening programme.

The majority of those screened get a **true-negative test result**, i.e. they are not sick and the test shows no abnormalities. For them, the impact of screening is very limited: they may experience some discomfort with the test and some may be anxious while waiting for the result. When screening with an annual or biannual LDCT scan, exposure to radiation is an additional drawback to consider, though.

3.2.2. False-positive, false-negative, indeterminate results and incidental findings

However, no test is 100% reliable, so a wrong or 'false' result is always possible. Some screened individuals are diagnosed with an abnormal result that later turns out to be false. This false alarm is called a **false-positive test result**. Indeed, the person concerned is offered additional tests, such as a biopsy and follow-up scans. These can be uncomfortable or cause complications (e.g. bleeding during a biopsy or infection as a result of the procedure). In addition, the thought of a possible tumour causes anxiety and thus reduced quality of life. The psychological consequences of a false-positive test can last for some time, and should not be underestimated.^{22, 23} The healthcare system and society also suffers from a false-positive result, as it requires the commitment of human and financial resources.

This also applies to an **indeterminate result**, which means that the first result is inconclusive, so that a new test is indicated earlier than the next screening round. Thus, further tests are needed in these people too, possibly resulting in a reduced quality of life.²⁴ Indeterminate results are therefore also considered a type of false-positive results in this report.

In the case of a **false-negative** result, the person does have a developing cancer, but it remains undetected. The screening result may give a false sense of security, making the person feel no need to consult a doctor when symptoms eventually appear. And when treatment is then initiated anyway, the disease is already more advanced, potentially resulting in more invasive procedures and a poorer prognosis.

A screening test can also reveal issues unrelated to the disease being screened for, so-called **incidental findings**. Since an LDCT scan provides an image of the entire chest, including organs such as the heart, thyroid, oesophagus and part of the upper abdominal organs, many different incidental findings are possible in lung cancer screening.^f

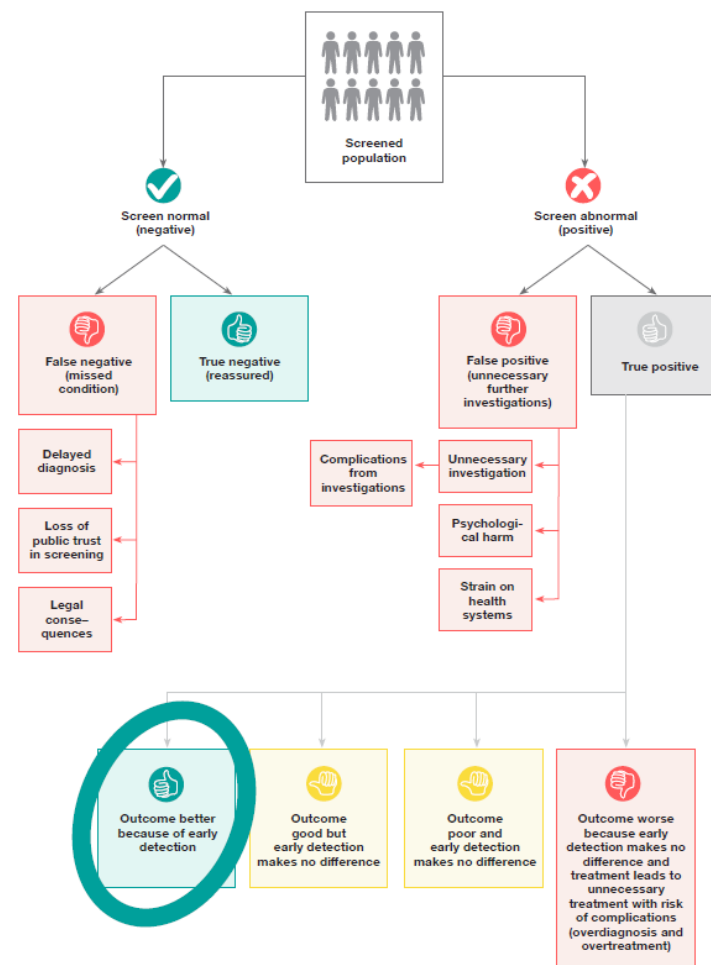
^f In this respect, lung cancer screening differs from, say, cervical cancer screening by smear or HPV test, or breast cancer screening with mammography, where the screening test better targets one organ.



These findings may lead to additional investigations and/or anxiety for screening participants. Some incidental findings may be beneficial for those participating in screening, such as early detection and treatment of an aortic aneurysm. Other incidental findings lead to anxiety, unnecessary medical interventions, risks and costs and ultimately provide no benefit to the participant, such as, for example, a liver lesion that turns out to be benign after biopsy.

The disadvantages associated with false and indeterminate results, and the consequences linked to incidental findings, must be taken into account when considering population screening.

Figure 2 – Possible results of a screening test



Source: World Health Organization (WHO) - Screening programmes: a short guide, 2020¹



3.2.3. Overdiagnosis and overtreatment

3.2.3.1. What is overdiagnosis?

One of the main drawbacks of population screening is overdiagnosis and overtreatment. This applies to the diagnosis and treatment of a tumour in the following three scenarios:

- A tumour that would have cured spontaneously;
- a 'dormant' tumour that grew very slowly or not at all, and which had posed no danger to the patient;
- a cancer that may evolve and become life-threatening, but occurs at a time when the patient is more likely to die earlier from another condition or from old age.²⁵

Overdiagnosis is considered a major disadvantage of screening as people are unnecessarily considered and treated as cancer patients (overtreatment), with the associated negative consequences on quality of life through fear, stigma and stress, side effects, costs for patients and society, e.g. through unnecessary medical procedures.²⁶

Overdiagnosis is difficult to understand and counterintuitive because in the individual patient, an overdiagnosed cancer cannot be distinguished from a cancer that would cause serious health problems without screening. People in whom a tumour is detected thanks to screening may be relieved and convinced that screening saved their lives, while they may have been unnecessarily labelled as a cancer patient and treated unnecessarily.

The risk of overdiagnosis and overtreatment should be clearly explained in advance to population screening participants.

3.2.3.2. How can the extent of overdiagnosis be calculated?

When a screening programme is initiated, one can expect an increase in the number of cancer diagnoses because they are detected earlier. Normally, the number of tumours at more advanced stages then decreases because they were detected earlier thanks to screening (the so-called *drop phenomenon*).

If incidence rates of early-stage cancer increase without a corresponding decrease in the number of diagnoses of tumours at more advanced stages, this may indicate overdiagnosis. Thus, the total number of tumours diagnosed should not increase over time.

Several methods exist to calculate overdiagnosis from cancer screening. More info on this can be found in Section 2.2.4 of the scientific report.

3.3. How to assess impact on survival and quality of life?

The ultimate goal of systematic cancer screening is to improve survival and quality of life. But how can we verify that this objective is ultimately achieved?

3.3.1. Improving mortality rates

Several outcome measures exist to measure whether a screening programme contributes to decreased mortality:

A reduction in disease-specific mortality (in this case lung cancer mortality) of those screened compared with those not screened is the main outcome measure in cancer screening clinical trials. However, determining cancer-specific mortality depends on identification of the cause of death, which is not always unambiguous and thus prone to bias. Moreover, this figure does not take into account possible deaths due to the screening itself (e.g. due to complications after surgery). The improvement in cancer-specific mortality may also give an overly optimistic picture of the impact of screening, if a cancer causes few deaths even without screening.²⁷



A reduction in overall mortality (from all causes, including lung cancer) of those screened compared to those not screened is the only outcome measure that answers the question of whether a screening programme actually saves lives.²⁸ Indeed, this so-called '*all-cause mortality*' takes into account all causes of mortality, including from early or late complications of treatment that may lead to mortality (which may not be recorded as lung cancer mortality). Thus, this outcome also includes the rare but possible mortality from investigating a false-positive result, or the mortality (whether increased or decreased) due to the diagnosis and treatment of incidental findings. For the above reasons, and if sufficient good-quality evidence is 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. More info on this can be found in Section 2.2.3 of the scientific report.

3.3.2. Improving quality of life

The aim of cancer screening programmes is not only to improve survival, but also to improve quality of life by avoiding heavy treatments for cancer in its highest stages. However, assessing the impact of a screening programme on quality of life is complex, partly because of the impact of the disadvantages of screening on quality of life. Waiting for results can cause anxiety and reduced quality of life, as can false-positive and indeterminate results (Section 3.2). A true-positive test result and subsequent investigations, treatments and complications can also reduce quality of life.

To properly assess this impact, longitudinal measurements are needed, using questionnaires to those invited.²⁹ These questionnaires should cover all steps in the screening process, such as deciding to participate or not, taking the test, receiving the result, dealing with it after an abnormal result, getting a diagnosis, etc.²⁹

Indeed, the decision whether or not to participate in screening can also cause stress. This decision can also cause psychological distress later, as people who do not participate and are later diagnosed with cancer may feel guilty.³⁰

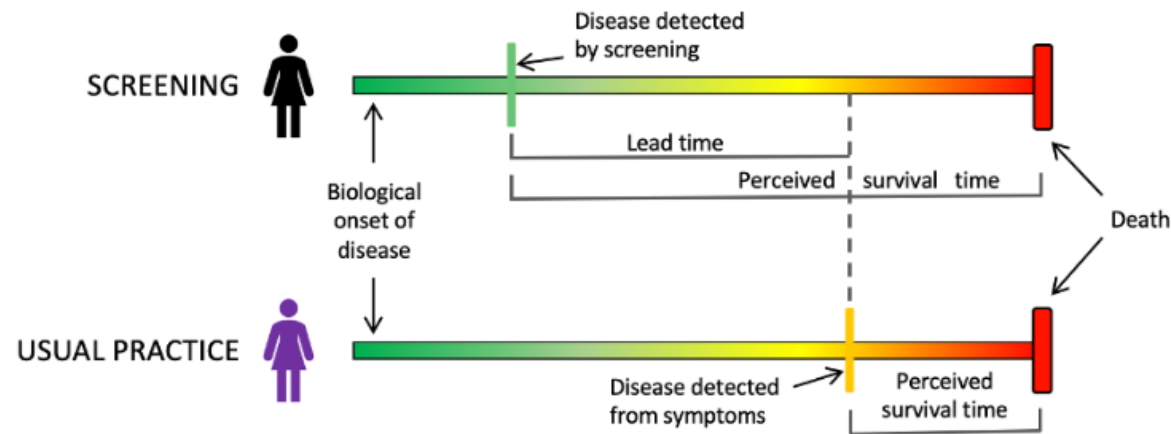
3.4. Pitfalls when assessing population screening

When considering a screening programme, several biases may give an overly optimistic picture of the benefits. These pitfalls should therefore be taken into account. Both '*lead-time bias*' and '*length-time bias*' overestimate the survival benefits of screening.

3.4.1. The '*lead-time bias*'

With a '*lead-time bias*', the survival of people diagnosed by screening is overestimated. In this case, early detection does not affect the course of the disease or the time of death (see Figure 3).³¹ But by calculating survival from the time the tumour is detected, it gives the impression that if the tumour was detected at screening, a person survives longer than if the disease is not detected until the onset of symptoms.

Figure 3 – Lead-time bias



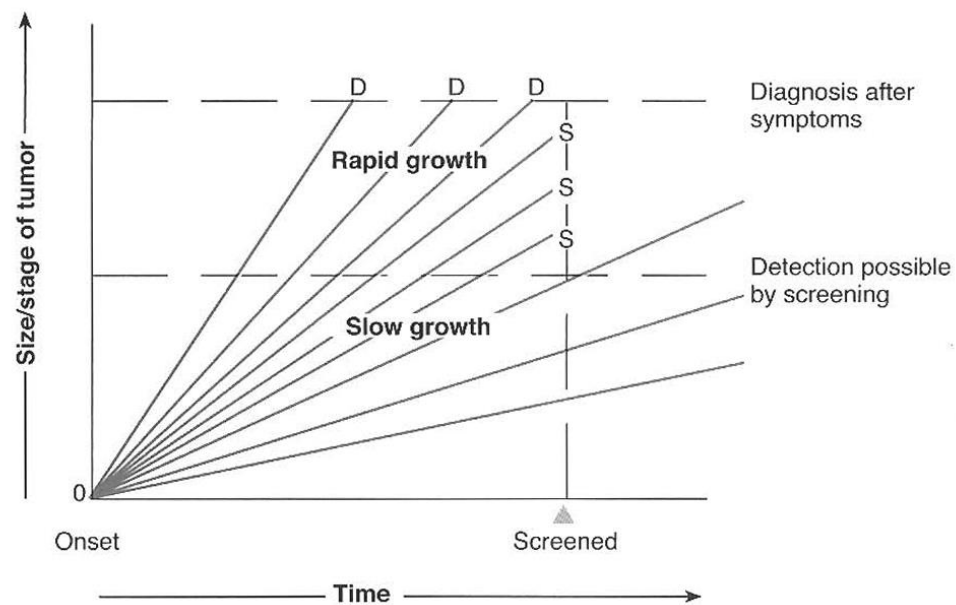
Source: Catalogue of Bias Collaboration, 2021³¹

3.4.2. The 'length time bias'

With a 'length time bias', the effect of screening on survival is overestimated because screening mainly detects slowly progressing tumours. Aggressive tumours are usually detected when symptoms appear, and this often occurs before the first screening or between screenings (**interval cancer**) (Figure 4).³² If one compares the survival of a tumour found by screening with tumours diagnosed after symptoms, one thus wrongly gets the impression that people live longer by screening.



Figure 4 – Relationship between length time bias and rate of tumour growth



Abbreviations: D = diagnosis after symptoms; S = detection after screening.
Source: Fletcher et al., 2005³³



4. IS LUNG CANCER SCREENING SAFE AND EFFECTIVE?

As always in a *Health Technology Assessment* (HTA, see Box 2), we first examine the safety and effectiveness of the technology, being lung cancer screening with LDCT in high-risk individuals. Lung cancer screening can be said to be effective if its benefits (reduced mortality and reduced burden of disease) outweigh the potential disadvantages of cancer screening, which we already discussed in the previous chapter.

To verify this safety and effectiveness, we conducted a systematic literature review. More information on our methodology can be found in Section 3.1 of the scientific report.

4.1. Does screening reduce mortality and disease burden?

The main objective of cancer screening is to save lives. As mentioned in Section 3.3.1, we initially look at overall mortality in those screened compared with those unscreened.

Research based on 8 different studies shows that screening with LDCT scan of persons at high risk of lung cancer reduces **overall mortality by 5%**. Taking into account the risk of mortality in this population, it was calculated that 210 people need to be screened to prevent one death from all causes.³⁴

When we look at lung cancer-related mortality, screening shows that this cancer-specific mortality decreases by 21%. The studies also point to a **sustained decrease in stage IV lung cancer**.

Lung cancer screening is thus effective in reducing lung cancer-specific mortality and overall mortality in those screened. Thanks to screening, the disease is less often diagnosed at an advanced stage, thus treatment is less burdensome and prognosis is often better.

4.2. Is there a positive impact on quality of life?

The health-related quality of life of those screened has only been measured in a limited number of studies, using questionnaires. However, this limited scientific evidence is not sufficient for our current study. We therefore conducted additional research for our Belgian economic evaluation (see further Chapter 6).

4.3. False-positive and false-negative results

The studies reviewed show that between 8% and 46% of the total number of participants required additional investigations at the first screening round, which we consider to be false positives. As mentioned above, these figures included indeterminate results. This percentage decreases with subsequent screening rounds. Studies show that 0.1%-1.7% of all screening participants require invasive procedures (e.g. biopsy or bronchoscopy) for a false-positive result. Only a limited number of studies investigated the complications that occurred during or after these procedures.

A small number of **false-negative results** were reported in the literature. On the one hand, this means that the consequences of these results are likely to be limited (e.g. being wrongly reassured), but also shows that not all lung cancers will be detected by screening at an early stage.

4.4. Overdiagnosis

As with the false-positive results, estimates for **overdiagnosis** varied very widely between studies: where one study reported no overdiagnosis at all,³⁵ another study found that as many as 67% of detected lung cancers would be overdiagnosed.³⁶ The majority of the other studies reported overdiagnosis between 20% and 25%. There are several factors of great importance in interpreting these figures, such as the duration of follow-up,³⁷ the characteristics of the screened population and the proportion of participants from the control group who also underwent screening during the follow-up period (so-called contamination of the control group).^{38, 39}



For our Belgian economic evaluation, different overdiagnosis figures are used in so-called scenarios to identify the impact on effectiveness and cost-effectiveness.

4.5. Incidental findings: an advantage or a disadvantage?

Incidental findings are frequent in LDCT screening participants, as a scan of the entire chest is performed. Some examples of incidental findings are renal cysts, thyroid lesions, arterial calcification, or an aortic aneurysm.

For several years, guidelines have been developed that allow for a standardised approach to reporting and dealing with such incidental findings. Based on such a guideline⁴⁰ and an analysis of the literature, we conducted **an exploratory analysis** to estimate how frequently incidental findings in LDCT screening would lead to additional investigations. We estimated that in **about 23% of screening participants, additional investigations would be indicated because of incidental findings**.

We emphasise that, based on the evidence, it is currently unclear to what extent these incidental findings ultimately result in health gain or loss for participants. For this reason, incidental findings cannot be included in calculating the cost-effectiveness of LDCT screening. Given their potential impact both on screening participants and the healthcare system, it is important to include them in the evaluation of LDCT screening. The use of standardised protocols for reporting and addressing incidental findings is recommended.

4.6. Radiation risk

Exposure to radioactive radiation from LDCT may increase the risk of cancer in the longer term, even if the dose is limited (see also Box 1). It is important to take this into account because only some of the participants benefit from screening, while all are exposed to the harmful radiation from LDCT. Assessment of cancer risk from radiation is done through complex modelling studies and only a few of the reviewed studies on lung cancer screening did such a calculation.

The German Federal Office for Radiation Protection published detailed and conservative estimates of the lifetime risk of cancer from repeated radiation in LDCT screening for a German population of heavy (former) smokers. This studied group is representative of a Western European population. When (ex-)smokers aged 50-75 years are screened annually with LDCT, the estimated lifetime risk of cancer from radiation is **less than 2.5 per 1000 women and about 1 per 1000 men**.⁴¹ Thus, the risk of cancer from radiation exposure in LDCT screening is significantly higher for women than for men.

Before organising a population survey using radiation (such as LDCT) in our country, a study must be mandated by the Federal Agency for Nuclear Control (FANC), the regulatory body for nuclear safety and radiation protection in Belgium, as stipulated in the Royal Decree of 13 February 2020 on medical exposures and non-medical imaging exposures with medical radiological equipment.⁴²



5. WHAT DOES THE LITERATURE SAY ABOUT THE COST-EFFECTIVENESS OF LUNG CANCER SCREENING?

In the next step of our analysis, we checked the cost-effectiveness of lung cancer screening with LDCT, using a systematic literature review.

5.1. Cost-effective, but....

All studies reviewed found that lung cancer screening imposes additional costs on the healthcare system, but also provides health benefits compared with usual care without lung cancer screening. With the exception of two studies, 17 of the 19 studies judged that lung cancer screening may be cost-effective compared to a situation without lung cancer screening.

Like the thresholds, the ICERs in the studies vary widely, from €1772 to €63 269 per QALY gained (see Box 4). Four studies also examined the cost-effectiveness of a smoking cessation programme combined with screening and found that it is even more cost-effective than screening alone.

Box 4 – What is cost-effectiveness? What is the ICER? What is a QALY?

A cost-effectiveness analysis (CEA) expresses the patient benefits of a given intervention in terms of life-years gained (LYG) or in life-years gained adjusted for quality of life (also called '*Quality-Adjusted Life-Year*' or QALY).

When a treatment is less expensive than those already in place, and provides a better outcome for the patient, the choice is easy. But often new treatments do offer health benefits, but cost more than conventional treatment. In that case, the ratio between the additional cost and the years of life gained (whether or not adjusted for quality of life) is calculated. This is called the ICER (*'incremental cost-effectiveness ratio'*), expressed as an amount per life year gained and per QALY gained.

No amount ('threshold value') has been set in Belgium on which to base a determination of when an intervention is too expensive in relation to the health gains achieved. Other countries, such as the UK, do use threshold values for the cost per QALY gained. When this cost per QALY gained is below £20 000, reimbursement of the intervention is rarely questioned. Between £20 000 and £30 000, there must be additional arguments for reimbursement and above £30 000, very strong arguments must be made.

5.2. ...studies with significant methodological shortcomings

In recent years, a large number of studies on the cost-effectiveness of lung cancer screening have been published worldwide. However, most of them have significant methodological shortcomings, which may lead to overly optimistic calculations of this cost-effectiveness.

Some examples of these limitations:

- In general, insufficient or even no attention was paid to the challenges and costs of selecting and inviting the target population, leading to an underestimation of screening costs. For our country, however, this would be one of the main organisational challenges since the government has no data on the smoking history of Belgian citizens.
- The majority of studies assume that all invitees will actually participate in screening, which is unrealistic. They do not take into account the identification and invitation costs of those who will not eventually participate and who will therefore not enjoy the health benefits and cost savings of screening. However, practice shows that not all citizens get screened for cancer. For example, the coverage rate of screening for colon, cervical and breast cancer in Flanders is around 65%.⁴³ For the Brussels region, this share is 28% for colorectal cancer and 53% for breast cancer (2020).⁴⁴ For Wallonia, recent data on cancer screening coverage are not publicly available.



- Although many studies rely on the two large randomised trials (NLST⁹ and NELSON) for effectiveness, a large number of studies deviate from the protocols of these studies (e.g. different screening intervals, different age groups, different smoking status). This is accompanied by considerable assumptions, which are not always based on evidence from quality scientific research.
- Most studies fail to take into account, or insufficiently take into account, a number of factors such as the impact of false-positive and indeterminate results, overdiagnosis, lead-time bias and incidental findings. However, these should ideally be included to reliably calculate cost-effectiveness.

Because of these limitations, and because of the lack of a study using Belgian cost data, this systematic literature review did not allow us to make reliable *evidence-based* recommendations on the cost-effectiveness of any lung cancer screening in Belgium. We therefore conducted our own cost-effectiveness analysis of lung cancer screening specifically for Belgium, as you can read in Chapter 6.

6. WOULD LUNG CANCER SCREENING BE COST-EFFECTIVE IN BELGIUM?

6.1. The results of a Dutch-Belgian study as a basis

In the previous chapter, we analysed the health economics literature on the cost-effectiveness of LDCT screening in high-risk adults compared with a situation without screening. However, we found that many of the reviewed studies faced methodological limitations.

We therefore decided to calculate the cost-effectiveness for Belgium. To do so, we used data from the NELSON Trial (see Box 5), supplemented by additional information from the literature and Belgian data on costs, survival and quality of life in the diagnosis and treatment of lung cancer.

We developed several scenarios and calculated the cost-effectiveness in each case. In the synthesis, you will find the base case scenario. In the scientific report, you will find the additional scenarios.

Box 5 – what is the NELSON study?

The NELSON study (Nederlands-Leuvens Lung Cancer Screening Study) is a pilot population-based study initiated in 2003. The aim was to investigate whether screening with LDCT reduces lung cancer mortality in high-risk individuals aged 50-74 years. Almost 16 000 people participated in the study, mostly men (84%).⁴ Six per cent of the participants were Belgian.⁴⁵ Screening took place at UZ Leuven and at three Dutch hospitals.

⁹ US National Lung Screening Trial
(<https://www.cancer.gov/types/lung/research/nlst>)

Participants in the screening group received four LDCT scans at increasing screening intervals



The NELSON study is the second largest (terminated) study on lung cancer screening, after the NLST, and, along with the latter, the only one that showed a significant reduction in lung cancer mortality thanks to lung cancer screening. One strength is that, unlike the NLST, it used a specific (so-called volumetric) protocol to evaluate lung tumour size. This resulted in fewer false-positive results. In addition to positive and negative results, a third category of 'indeterminate' findings was also used to minimise the number of false-positive screening results. Detailed information was available for all these outcomes, as well as on additional examinations and complications that occurred.³ We also use information on the number of screen-detected cancers, interval cancers, including their staging and histology as input for our analysis.^{2-4, 45, 46}

There are also some important limitations. The determination of cause of death in study participants was not always done in the same way,³⁴ which poses a risk of bias in determining cancer-specific mortality (see 3.3.1). Women constituted only 16% of participants, and were thus underrepresented. The results of female participants were also not included in the published results.⁴ However, these were provided to us by the NELSON researchers. Only after the study began, a fourth screening round after an interval of 2.5 years was added. Different estimates for overdiagnosis were reported for the NELSON study; we include these in the model in different scenarios. For information on overdiagnosis in NELSON, please refer to Section 6.2.7 and to the scientific report.

6.2. What inputs did we use for our model?

6.2.1. The population to be screened

Almost all included studies only invited (ex-)smokers for screening.

For the population to be screened, we based ourselves on the population from the NELSON study, applying the following inclusion criteria:

- People aged between 50 and 75 years AND one of the following three;
- Smokers who have smoked at least 10 cigarettes a day for at least 30 years;
- Or smokers who have smoked at least 15 cigarettes a day for at least 25 years;
- Or former smokers with such a smoking history who had quit smoking less than 10 years ago.

We could not model the impact of a possible adjustment of admission criteria, which is a limitation of our analysis. However, it can be estimated based on trends in the literature, and on logical reasoning. The risk of lung cancer increases with age, so lowering the minimum age limit is likely to have a negative impact on cost-effectiveness. Increasing the maximum age increases the risk of overdiagnosis, possibly resulting in less favourable cost-effectiveness.



6.2.2. The screening intervals

We relied on the screening intervals from the NELSON study. The NELSON study used an interval of first 1 year, then 2 years, and provided a fourth screening after 2.5 years.⁴

The NELSON study reported an increased number of stage IV interval cancers after the 2.5-year interval. It suggests that the latter interval leads to reduced efficacy.⁴⁶ Also because experts have indicated that a 2.5-year interval is not currently under consideration, we decided not to include this last screening round in our model. Our model thus includes three screening rounds, with a 1-year interval between the first two screening rounds and a 2-year interval between the second and third rounds.

Based on the available evidence, there is currently uncertainty about the effect on mortality of biennial compared to annual screening. These uncertainties are reflected in the wording of the European Technical Standard of the European Respiratory Society:⁴⁷

- *"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."*

We have not calculated the cost-effectiveness of annual screening, but it is likely to be less favourable. Indeed, the number of interval cancers detected in the second year of the interval in the NELSON study appears to be small compared to the additional cost of annual screening. In addition, one must also consider the organisational and budgetary impact of annual screening.

To be more certain about the effect of shortening the screening interval, additional evidence is needed from future and/or ongoing studies, such as the 4-IN-THE-LUNG-RUN study. In this study, annual and biannual screenings are compared, in participants with normal initial screening.⁴⁸

6.2.3. Participation in screening

A challenge in lung cancer screening is that data on the individual smoking behaviour of the Belgian population are not available in any administrative database. Thus, a much broader group is addressed to finally reach the correct target population. In the NELSON study, a questionnaire was initially sent to more than 606 000 people. After an initial response from about ¼ of this group, about 31 000 people met the inclusion criteria. Of these, about half (15 822 people or 51.1%) participated in the study.

Our model used the participation rate of 51.1% from the NELSON study. Of course, this is only an indication and the willingness to participate in targeted population screening may be higher or lower. To determine the impact of the participation rate on cost-effectiveness, scenarios were calculated with higher and lower participation rates. In addition, a scenario was also calculated where participation in the second and third rounds is lower than in the NELSON study.

6.2.4. False positives, indeterminate results and incidental findings

Besides overdiagnosis, false-positive and indeterminate results are major drawbacks of lung cancer screening. Yet only a handful of the economic studies we reviewed took this into account. In our model, we attribute both costs and a temporary loss of quality of life to these results due to the overtreatment, additional investigations, anxiety and stress (see Section 3.2), based on data from the NELSON study. We did not include the impact of incidental findings in our model because reliable evidence on its impact is lacking. It will be associated with additional costs anyway, but it is not clear whether it also leads to health benefits or harms.



6.2.5. Interval cancers

There are cancers that will manifest between screenings (interval cancers). The information on interval cancers is taken from the NELSON study. Since these were not detected by the lung cancer screening, we assume that they will be diagnosed at the same time as in unscreened individuals. As a result, no additional costs or effects for interval cancers are included in the economic model (they cause the same costs and effects in both groups).

6.2.6. Lung cancer stages

The aim of lung cancer screening is that lung cancers are detected at an earlier stage ('stage shift'), leading to a higher chance of successful treatment and improved survival. The number of cancers detected by lung cancer screening, as well as their stage and type of cancer, is based on information from the NELSON study. We also used the information from the NELSON study for the control group.

6.2.7. Overdiagnosis

Half of the economic studies we reviewed did not take overdiagnosis into account, leading to overly optimistic ICERs. By definition, overdiagnosed cancers do not lead to a survival benefit for the participant, so costs were charged for this percentage of screen-detected cancers, but no survival benefit.

In our analysis, we modelled scenarios with different overdiagnosis rates to account for the existing uncertainty around overdiagnosis. NELSON published an overdiagnosis estimate of 19.7% for male participants at 4.5 years after the last screening round,⁴ for female participants, overdiagnosis at this time was 45% (unpublished data). One year later, i.e. 5.5 years after the last screen, it was still only 8.9% for the men, while no data are available for the women.^h For the base case in our model, we used the combined figures for men and women at 4.5 years, being 23.9%. To calculate the

impact on cost-effectiveness, we modelled additional scenarios with more positive estimates of 8.9% (based on the data on men in the NELSON study), as well as a scenario with a more negative estimate of 38%. For more information on this, please refer to the scientific report.

6.2.8. Survival

From the BCR, we obtained information on survival time after diagnosis of lung cancer, by stage and type of cancer, based on diagnoses made between the years 2015 to 2020. Patients aged between 50 and 74 years were selected, as was the population in NELSON. More details can be found in Chapter 5 of the scientific report.

Based on BCR survival data, survival could be determined as a function of lung cancer stages and type of cancer. Linking this information to the 'stage shift' allowed us to calculate the gain in life years.

6.2.9. Quality of life

Screening for lung cancer can have both positive (through detection of the tumour at an earlier stage) and negative effects on quality of life (through false-positive or indeterminate results and overdiagnosis). Although quality of life should be considered a relevant endpoint in clinical trials, the evidence in the NELSON study is limited. We could rely on NELSON only for short-term reduced quality of life linked to false-positive or indeterminate results. For further information on quality of life as a function of lung cancer stages, we relied on information from a targeted (non-systematic) search strategy for reviews on quality of life in lung cancer patients and information from the economic literature review (Chapter 5).

^h 8.9% is mentioned by the NELSON authors as a possible upper limit for overdiagnosis. Given the absent data on contamination and the higher

overdiagnosis rates for the women in the study, we use a more conservative assumption as the base case in our model.



We used the values for quality of life (*health utilities*) from Tramontano et al.⁴⁹ for our baseline model. Since participation in lung cancer screening is voluntary, we assume that participation itself has no negative impact on quality of life. Due to a lack of evidence on the impact of overdiagnosis on quality of life, we did not consider it in our model.

6.2.10. Cost

Data on the costs of **identification and invitation for screening** were provided to us by the Flanders Department of Care, based on their experience with and information on existing screening programmes. These costs were verified by an expert from the relevant departments of the other federated entities.

We based the cost of **LDCT scans** on the 2024 NIHDI nomenclature.

A strength of our analysis is that we were able to rely on recent data from the Belgian Cancer Registry (BCR) coupled with reimbursement data from the Intermutualistic Agency (IMA) for the costs of **diagnosis and treatment** of lung cancer. By excluding from our sample patients who had already been diagnosed with another cancer prior to the lung cancer diagnosis, we were able to obtain the most accurate data possible of the costs linked to lung cancer. Indeed, the data do not allow us to distinguish e.g. between radiotherapy for lung cancer and radiotherapy for another cancer, if these treatments were given in the same period.

The BCR data included almost all cancer cases in Belgium, and the linked data allowed to determine the actual costs of diagnosis, staging and treatment estimated by stage and histology, for a large sample of patients over a long period of time.

Based on the IMA data, the following costs were determined:

- Diagnostic and staging examinations (imaging, biopsy);
- Cost of lung cancer-related surgery and all costs of hospitalisation during which the surgery took place;
- Cost of systemic therapyⁱ and all costs charged on the day of administration (e.g. day hospitalisation, supportive medication);
- Cost of radiotherapy based on specific nomenclature codes;
- Costs related to palliative care based on specific nomenclature codes.

A limitation, in turn, is that it takes 2 years for the data to be fully available in the IMA database. As a result, for the most recent year (2020), we could only use costs for the first year after diagnosis. For the longer follow-up, we relied on data from the full sample (patients diagnosed with lung cancer in 2015 or later). We also did not have the costs of treating complications after discharge, as these could not be reliably identified in the IMA data.

We are also unaware of the confidential price discounts on lung cancer treatments that were reimbursed under '*managed entry agreements*' between government and pharmaceutical industry. We used a 40% price discount for our model (see Box 6). In the scientific report (Chapter 6), you will also find other analyses with discounts of up to 90%, allowing policymakers to extract the cost-effectiveness at each order of magnitude of discount.

We supplemented the BCR and IMA data with information from the NELSON study (e.g. number of interventions performed after false-positive and indeterminate results) and applied Belgian rates to them, based on the NIHDI nomenclature.

ⁱ Chemotherapy, hormone therapy, targeted therapy and immunotherapy.



Frame 6 – the confidential price discounts in *managed entry agreements*

A limitation of the cost data we used is that it only reflects the official prices of a medical intervention. However, most expensive systemic therapies are reimbursed under a so-called *managed entry agreement*, in which confidential price discounts are negotiated between the pharmaceutical company and the government. As a result, we cannot use the exact price discounts in our model. However, it is a certainty that there are price discounts. Hence, it would be incorrect not to include them in the model. The question then becomes how big this discount is.

The MORSE report⁵⁰ does state the average discount given in a given year for all products reimbursed under a *managed entry agreement*.

The first-year costs in the model are based on these costs for diagnosed cancers in 2020. The discount in 2021 averaged over 50%. In 2020, it averaged 40%. Although most of the systemic therapy costs relate to immunotherapy drugs and targeted therapies, not all products in our sample are drugs reimbursed under a *managed entry agreement*. On the other hand, the price discount of individual products can easily be much higher/lower than the published average. Thus, the 40% average price discount we used is an informed estimate about the actual average price discount.

In our scientific report (Chapter 6), you will also find other scenarios where we applied different price discounts. That way, the policymaker, knowing the actual price discount for individual products, can better determine which ICERs best reflect reality.

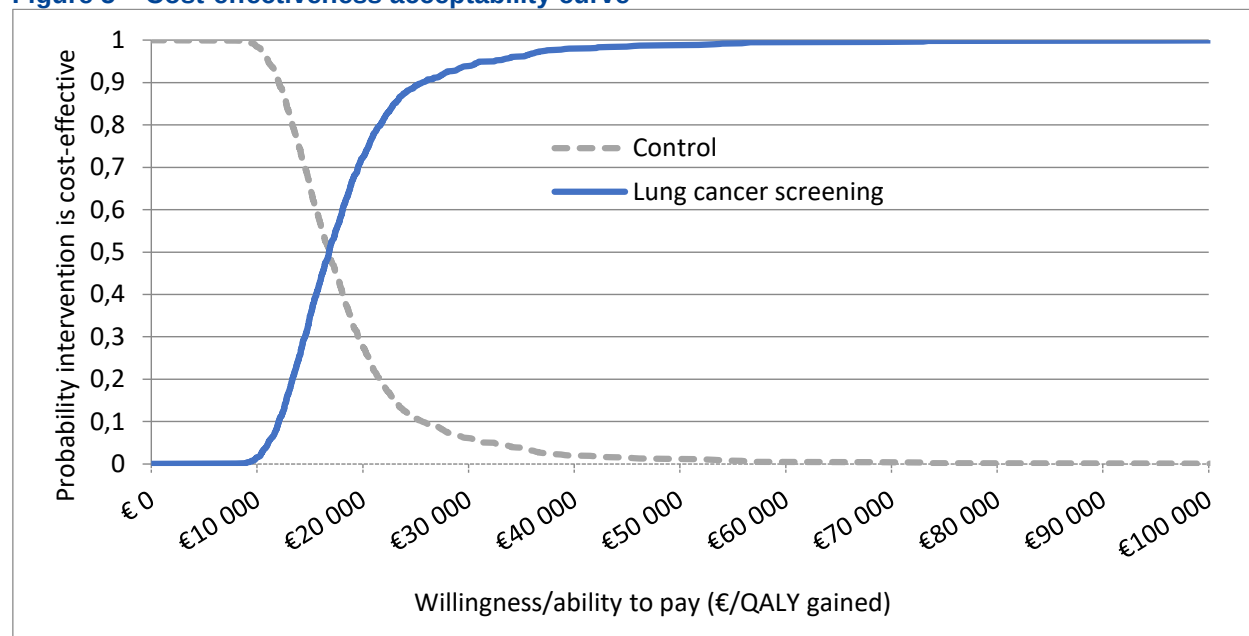
6.2.11. Belgian guidelines

For our economic model, we relied on a lifetime time horizon with a discount rate of 3% for costs and 1.5% for effects, according to Belgian guidelines for health economic evaluations. The evaluation was conducted from the perspective of the healthcare payer with costs taken into account for the government and patient. The guidelines indicate that patient supplements should not be added in the base case. An additional analysis determined the impact of adding these supplements.

6.3. Results of our economic analysis

Because it is not clear how many participants would participate in lung cancer screening, and to simplify interpretation, we expressed the results per 100 participants. Our baseline analysis shows that lung cancer screening would result in an incremental cost of €77 747/100 participants and 4.64 QALYs gained/100 participants. This equates to an ICER of €18 530/QALY gained compared to no lung cancer screening. This scenario assumes a participation rate as in NELSON (51%), a lifetime time horizon including discount rates according to the Belgian guideline, an overdiagnosis rate of 23.9%, and a price discount for systemic therapy of 40%.

The *cost-effectiveness acceptability curve* indicates that at a willingness to pay (see Box 4) of e.g. €10 000 per QALY gained, there is a 1.5% probability that lung cancer screening is cost-effective. At €20 000 per QALY gained, this probability is 72%. If the willingness to pay was €30 000 per QALY gained, this probability increases to 94%.

**Figure 5 – Cost-effectiveness acceptability curve**

6.4. Key variables with impact on ICER

A number of variables have a significant impact on the ICER. Besides the time horizon and discounting, this is especially the case for the number of overdiagnoses. Increasing the overdiagnosis rate from 23.87% to 38% would increase the ICER from €18 530 per QALY gained to €27 712 per QALY gained. In turn, a lower overdiagnosis rate of 8.87% would lower the ICER to €11 850 per QALY gained.

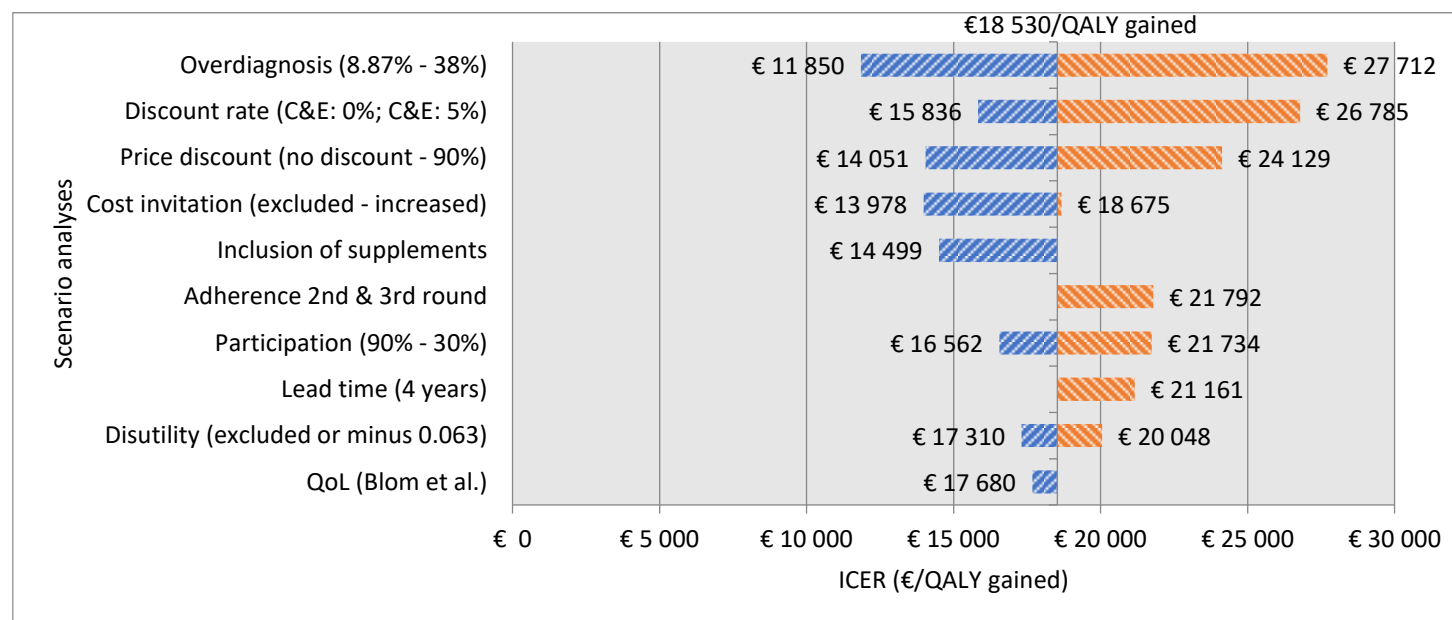
Next, price discounts for systemic therapy (see Box 6) have a strong influence on the ICER. The higher these discounts, the less cost-effective lung cancer screening becomes, and vice versa. Without applying the price discounts, the savings from screening (by avoiding the more expensive

treatments) are overstated. If a better estimate (through the NIHDl) of the actual discount could be made, an even more precise estimate of the ICER could be made.

The tornado diagram also shows the importance of taking into account the cost of reaching and inviting participants. Unjustly excluding this cost, as was the case in several previous economic evaluations, results in overly optimistic ICERs.

There are also variables with a smaller impact, such as the participation rate throughout the screening programme. However, combining multiple scenarios may obviously have a higher overall impact on cost-effectiveness than the impact of the variables separately. Finally, changing the loss of quality of life due to false positives and indeterminate results, as well as changing the values for quality of life based on Blom et al.⁵¹ have a relatively small impact on the ICER.

Figure 6 – Tornado diagram showing key cost-effectiveness variables





6.5. Weighing pros and cons: the 1000-person figure

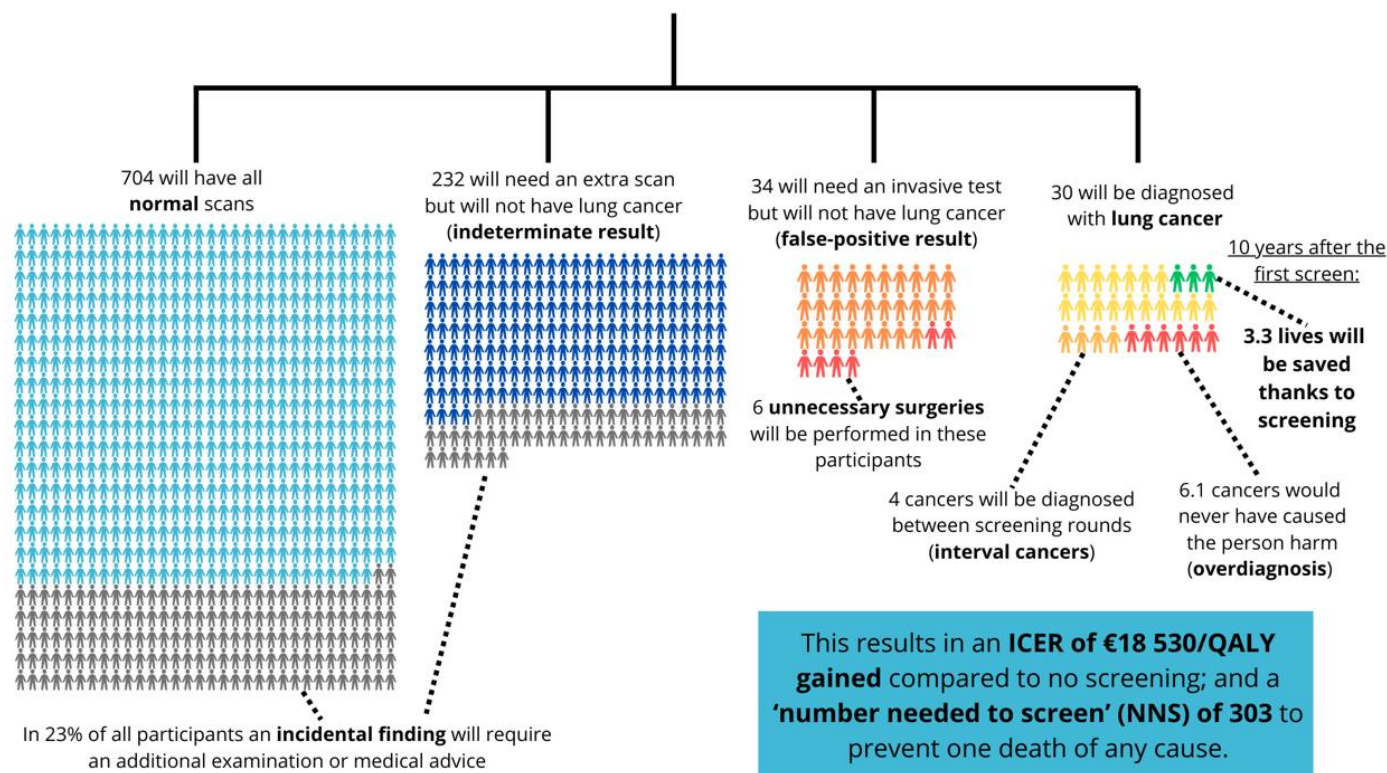
When considering lung cancer screening, besides assessing cost-effectiveness, it is also crucial for policymakers to consider all pros and cons. A commonly used method to compare these pros and cons side by side is a 1000-person figure. It is useful for policymakers when making a decision to organise screening. The results of the basic analysis of our health economic evaluation are presented in **Error! Reference source not found.**⁷.

Furthermore, the policymaker should also take into account other elements, including the capacity of equipment and healthcare staff. (see Section 8).

If a decision is then made to organise screening, citizens should then be given the opportunity to make their own informed personal decision about their participation.⁵² The 1000-person figure can also be used for this purpose.

Figure 7 – 1000-person figure of the KCE base case analysis

LDCT screening has potential benefits and harms. When screening 1000 high-risk individuals 3 times, we estimate that:



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 biopsy or bronchoscopy. The information to form mutually exclusive groups after three rounds of screening is from Horeweg et al.² Information on the number of surgeries for false positives is from van 't Westeinde et al.³

Note: The 1000-person figure is also available for other scenarios of overdiagnosis in our scientific report.



The following information is not presented in the 1000-person figure for simplicity of presentation, but is also important when evaluating LDCT screening:

- Radiation risk was not included as it was not modelled for 3 rounds of screening and a 10-year follow-up.
- Complications for 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.³
- For the incidental findings, we rely on our exploratory analysis (see Section 4.5). The potential health gain - or loss could thus not be modelled.

The difference in mortality after 10 years in our model approximates the result of a systematic review³⁴ of good quality. Therefore, we are confident that our model provides plausible results. More details on this validation of our model can be found in Chapter 6 of the scientific report.

7. ETHICAL ASPECTS OF LUNG CANCER SCREENING

The decision to organise systematic cancer screening must also take into account a number of ethical aspects. Lung cancer screening poses further specific ethical challenges in this regard because it targets specific populations.

7.1. Ethics in healthcare in general

Ethics play a central role in healthcare. The most well-known are the four ethical principles of Beauchamps and Childress:⁵³

- **Principle of respect for autonomy:** individuals should be able to make informed decisions about their own lives and health. Healthcare providers should respect the patient's choice and involve them in the decision-making process.
- **Principle of beneficence:** the healthcare provider must act in the patient's best interests. In doing so, he/she should maximise benefits and minimise harm. The aim is to ensure patient well-being and promote positive outcomes.
- **Principle of non-maleficence:** the healthcare provider must not cause harm and must minimise the risks of medical interventions.
- **Principle of justice:** benefits and burdens in society should be shared fairly, including in healthcare. Equal access to healthcare should be guaranteed and all forms of discrimination should be avoided.

These fundamental principles can also be applied to lung cancer screening.

7.2. Ethics in screening linked to individual behaviour

Lung cancer screening with LDCT typically targets high-risk adults, and especially (former) smokers. This linking of cancer screening to individual behaviour, such as smoking, raises specific ethical challenges in addition to the principles we described above.



7.2.1. Fairness in defining target group

Determining the right target population is essential for an effective screening programme. In the case of lung cancer screening, choosing (former) smokers as the target population may raise ethical questions, as it may exclude other high-risk groups. Examples include people who were regularly exposed to hazardous substances such as asbestos, passive smokers, or people with a family history of lung cancer.^{54, 55} This exclusion may be considered unfair.

This can be accommodated by multivariable models that calculate the risk of lung cancer over a given period and use a risk threshold to determine who is eligible for screening. Several risk prediction models take into account, in addition to smoking behaviour, e.g. family history of lung cancer, asbestos exposure and chronic obstructive pulmonary disease (COPD).¹⁹

7.2.2. Accessibility, transparency and informed consent

The effectiveness of lung cancer screening also depends on the number of participants.⁵⁵ However, there appear to be more barriers to reaching and achieving sufficient participation of the target audience than in other screening programmes such as breast, cervical and colorectal cancer screening.

People from vulnerable socio-economic groups are more likely to get lung cancer because they are more likely to smoke or doing unhealthy jobs. They would therefore benefit most from lung cancer screening. Yet they are often harder to reach or decide not to participate in screening. Smokers sometimes feel guilt about their smoking behaviour and fear the test result. As a result, they often avoid information about the risk of smoking and lung cancer screening.⁵⁵⁻⁵⁷ Furthermore, they often distrust the health system and the government and struggle with lower health literacy.

Recent research explored which effective strategies can increase this accessibility. Important are targeted outreach, working with local institutions or advocacy groups, and appropriate communication when inviting and providing information about lung cancer screening.^{58, 59} Lack of transparency about potential harm is an ethical concern for screening programmes, as it directly conflicts with the principle of autonomy and informed consent.

Community initiatives and use of digital technology can improve accessibility in remote or disadvantaged areas, but at the same time it can be a barrier for vulnerable socio-economic groups, as they are often less familiar with digital communication.

7.2.3. Risk of feeling stigmatised

There may be a perception among some that smokers with lung cancer are themselves responsible for their disease. As lung cancer screening invites mostly heavy smokers, the risk of stigma is therefore high. Research has shown that these people often feel unfairly treated because they are invited because of their behaviour, while other factors can also cause lung cancer.⁵⁵



7.2.4. Risk of unwanted behaviour

There are no objective figures on individual smoking behaviour, but one has to rely on what the smoker reports himself. People may present their behaviour differently for two different reasons:

- Out of concern, exaggerate (past) smoking behaviour to still qualify for screening.
- Downplaying (past) smoking behaviour to avoid being invited, so as not to face the social stigma of being a smoker or not wanting to face a diagnosis due to fear.⁶⁰

This phenomenon can distort the selection of the right target group, and undermines the accuracy and effectiveness of the screening programme.

Discussions are also ongoing around the so-called 'free pass to smoke'.⁶⁰ It implies that people assume that lung cancer screening will allow them to continue smoking because a tumour will be detected early by screening anyway. A smoking cessation is then less necessary, according to their reasoning. This raises ethical questions about the unintended consequences of screening.⁶¹

7.3. Conclusion

Systematic screening for lung cancer in Belgium targeting hard-to-reach populations must be equitable, accessible and transparent, with clear communication adapted to the target group. It must also take into account possible stigmatisation and undesirable behaviour.

Finding a delicate balance between the benefits of early detection of lung cancer, and the ethical considerations in selecting individuals based on their behaviour, is crucial in any implementation of lung cancer screening.

8. IMPORTANT ELEMENTS BEYOND THE SCOPE OF OUR STUDY

Besides a thorough assessment of the effectiveness and cost-effectiveness of a screening programme, other factors such as the impact on the health budget and system should also be taken into account.¹ In addition, combination with smoking cessation can still significantly affect cost-effectiveness, and quality assurance of a screening programme is crucial for a lung cancer screening programme.

8.1.1. Impact on the budget

From an economic point of view, when advising on the efficient use of limited resources, priority should be given to the cost-effectiveness of an intervention (i.e. the expected cost of the intervention relative to the expected effects). Already based on our information on safety/efficacy and cost-effectiveness of lung cancer screening, the policymaker can decide whether to consider lung cancer screening. Because the impact on the budget depends on a number of policy choices yet to be made (e.g. screening interval, population, invitation procedure, etc), we did not calculate the financial impact of the screening programme on the healthcare system. If policy makers decide to organise lung cancer screening, including the above-mentioned policy choices, a budget impact analysis can be carried out in the next step, based on this report.



8.1.2. *Impact on health system*

Population screening requires not only sufficient financial resources, but also the necessary infrastructure and capacity of healthcare staff. It is therefore necessary to identify which people and services will be involved in the process, and whether there is sufficient capacity for this.

Healthcare providers who play an important role in recruiting and informing participants must have sufficient knowledge and time. Incidental findings will require additional medical interventions. Therefore, protocols should be developed for their reporting and management.

Another important requirement is sufficient capacity for LDCT scans, and concerns have been raised about this for Belgium.⁶² The potential impact on waiting times for CT scans should be assessed before considering lung cancer screening. Remarkably, the Swiss Cancer Screening Committee recommends biennial screening just because of capacity problems with annual screening.⁶³

8.1.3. *Combination with smoking cessation*

This KCE report deals only with lung cancer screening and the economic model did not take into account the combination with a smoking cessation programme. Research shows that combining LDCT with effective smoking cessation programmes further reduces mortality from lung cancer and other tobacco-related diseases⁶⁴ and that it also benefits cost-effectiveness.⁶⁵⁻⁶⁸ Smoking cessation interventions are already available to the population and are considered cost-effective. If lung cancer screening were to be organised in Belgium, it would best be combined with existing smoking cessation interventions.

8.1.4. *Quality monitoring*

One of Dobrow's principles (see Section 2.2 in the scientific report) states that a screening programme should be continuously monitored, to support the most effective screening and to gain and maintain public trust.^{1, 69} This requires a high-performance ICT system and continuous data collection. Screening standards should also be developed using outcome measures such as tumours detected, number of false-positive results, harm from invasive procedures, etc.^{69, 70} Furthermore, audits of reporting and management of incidental findings and training for radiologists could be included in quality assurance for lung cancer screening.⁷⁰ The the federated entities, which are responsible for organising screening programmes, have experience with this.



9. CONCLUSION

Lung cancer is one of the most common cancers in Belgium. Because most tumours are at an advanced stage at diagnosis, it is also one of the deadliest cancers. If lung cancer is treated at an early stage, patients have a much better prognosis. For this reason, early detection by screening individuals at high risk of lung cancer with low-dose CT scan (LDCT) may be useful to reduce disease burden and mortality.

Before launching this population screening in our country, KCE was asked to assess whether lung cancer screening in a high-risk population is cost-effective. To estimate this cost-effectiveness, effectiveness and safety must first be assessed. Based on this information, supplemented with Belgian data, a cost-effectiveness analysis was carried out.

9.1. Is lung cancer screening effective and safe?

9.1.1. *Benefits: fewer advanced cancers and reduction in deaths*

The main objective of cancer screening is to save lives. Our literature review showed a **21% reduction in lung cancer-specific mortality** among participants. When all causes of mortality are taken into account, we see a **5% decrease in overall mortality** for this population. Moreover, the incidence of stage IV lung cancer decreases because the tumours are detected at an earlier stage.

Based on our cost-effectiveness analysis, we estimate that if 1000 high-risk individuals participate in three rounds of screening, three lives will be saved after 10 years thanks to this screening.

9.1.2. *Disadvantages: indeterminate and false-positive results, overdiagnosis and radiation exposure*

Despite the above benefits, a number of participants also experience harm from screening, as is the case with all cancer screenings.

Based on our analysis, we estimate that after three rounds of screening, almost 1 in 4 participants (23%) will need an additional scan to rule out lung cancer, following an **indeterminate result**. Moreover, about 3% of participants will face a **false-positive result**, leading to unnecessary invasive investigations (e.g. biopsy, bronchoscopy, or even surgery) and, in rare cases, complications.

It is important to point out that not all lung cancers are detected by screening: so-called **interval cancers** manifest themselves between two rounds of screening.

Lung cancer screening also certainly involves **overdiagnosis**, diagnosing and treating a cancer that would never have caused problems. However, there is uncertainty about the exact extent. Our literature review shows that most studies report overdiagnosis between 20% and 25% of cancers detected. In our baseline analysis, we assumed an overdiagnosis rate of 23.9%. Scenarios were also run with more optimistic and pessimistic figures for overdiagnosis.

Finally, there is also a **radiation risk** associated with repeated LDCT scans. If we assume that in our country (former) smokers between 50 and 75 years of age will be invited annually for lung cancer screening, the estimated lifetime risk of cancer from radiation is less than 2.5 per 1000 women and about 1 per 1000 men.⁴¹ The risk of cancer from radiation is significantly higher in women than in men.



9.1.3. *And what about incidental findings?*

Lung cancer screening can also reveal findings unrelated to the disease being screened for, known as **incidental findings**. We estimated that 23% of screening participants would need an additional examination or medical advice for incidental findings.

Further research is needed to calculate the health gain or loss of these incidental findings, but it is clear that a significant proportion of participants will require additional investigations, which may lead to additional morbidity and impact on quality of life. As these findings may also have a significant impact on the healthcare system, they should also be taken into account.

9.1.4. *Important advantages and disadvantages to be communicated to the target group in advance*

We note that both the benefits of reducing (lung cancer-specific) mortality and the drawbacks of overdiagnosis and false-positive testing, in particular, are important. It is therefore appropriate to provide full and clear information on this to all potential participants, even if this would lead to a lower number of participants.⁶⁰ A number of ethical aspects should be taken into account when providing this information (see Chapter 7).

A commonly used method for displaying information about lung cancer screening, is the use of a 1000-person figure (see Figure 7). Since such a figure represents the ratio of possible pros and cons, there is no "right" choice to be made, but individuals are encouraged to make their own informed personal decision about their participation in lung cancer screening.⁵²

9.2. *Would lung cancer screening be cost-effective in Belgium ?*

9.2.1. *According to the international literature reviewed*

Although a considerable number of studies have been published in recent years on the cost-effectiveness of lung cancer screening, most of them have significant methodological shortcomings. For instance, the aforementioned disadvantages of screening, as well as the cost of inviting participants, were not always taken into account, which may lead to overly optimistic estimates of cost-effectiveness. For this reason, we conducted our own cost-effectiveness analysis of lung cancer screening for high-risk individuals for our country, compared with no lung cancer screening.

9.2.2. *Based on our own analysis for the Belgian context*

Good-quality scientific evidence from randomised studies, combined with recent and complete Belgian *real-world* data from the BCR and IMA, allowed us to develop a reliable economic evaluation.

We found that lung cancer screening in Belgium would result in an incremental cost of €77 747/100 participants and 4.64 QALYs gained/100 participants. This amounts to an ICER of €18 530/QALY gained, compared with no lung cancer screening. A number of variables have a significant impact on the ICER, such as the number of overdiagnoses, price discounts on cancer therapies, the costs to reach participants, and the number of participants.

The *cost-effectiveness acceptability curve* indicates that at a willingness to pay (see Box 4) of €10 000 per QALY gained, there is a 1.5% probability that lung cancer screening is cost-effective. If the willingness to pay is €20 000 or €30 000 per QALY gained, this probability is 72% or 94%, respectively.



9.3. Overall conclusion

Screening for lung cancer with LDCT in high-risk individuals can reduce lung cancer-specific mortality and overall mortality of participants, but potential disadvantages must be taken into account, especially those of overdiagnosis and false-positive results. LDCT also involves a significant number of incidental findings, the overall pros and cons of which are unknown. Furthermore, each participant is also exposed to radiation.

Lung cancer screening may be cost-effective if the government's willingness to pay is between €20 000 and €30 000 per QALY gained. Notwithstanding lung cancer screening can be cost-effective, the balance between clinical advantages and disadvantages is less clear-cut and needs to be carefully weighed against each other by policymakers. The impact on available budgets and capacity within the healthcare system also play an important role here. Finally, if a screening programme is initiated, each participant should be clearly informed about the pros and cons in advance so that they can make an informed decision. This ethical obligation should be respected, even if this reduces the participation rate.



■ RECOMMENDATIONS^j

The following recommendations are addressed to the Ministers of Welfare and Health and administrations of the federated entities, responsible for funding and implementing population screening.

1. General recommendations related to effectiveness:

- 1.1. We recommend that when deciding whether or not to introduce lung cancer screening in (former) smokers at high risk of lung cancer, the effectiveness and expected health benefits are weighed against the expected harms for participants.
- 1.2. Factors to consider include indeterminate or false-positive findings, overdiagnosis, impact on overall mortality and quality of life, radiation risks and incidental findings.
- 1.3. Because of the complexity, we recommend using the 1000-person figure developed based on the available evidence.
- 1.4. The policymaker should investigate the willingness of the target group to participate in lung cancer screening when they are informed based on the 1000-person figure.

If the policymaker were to consider lung cancer screening following the effectiveness assessment mentioned above, the following elements should then also be taken into account: cost-effectiveness, budget impact, and organizational implications.

2. Cost-effectiveness:

Based on health economics considerations, if willingness to pay is sufficiently high, lung cancer screening could be considered.

3. Budget impact:

As a function of the envisaged lung cancer screening programme, we recommend taking into account the impact on the budget of the different actors within the health care system.

4. Organisational impact:

- 4.1. Before lung cancer screening can be introduced on a large scale, the organisational impact of such a programme should be estimated, both in terms of availability of infrastructure and

^j The KCE alone is responsible for the recommendations.



the required capacity of healthcare staff. In doing so, we also recommend assessing the potential impact on other care activities (e.g. on waiting lists).

4.2. In particular, the impact of different approaches in the management of incidental findings on the above elements should also be evaluated.

5. Initially, consideration should be given to whether lung cancer screening should be introduced. The following recommendations are therefore conditional. If the decision is made to introduce this screening, we recommend:

5.1. Integrate smoking cessation interventions into lung cancer screening. We recommend elaborating the choice and implementation of these smoking cessation interventions with all stakeholders involved.

5.2. Establish a clear protocol for the management of incidental findings. In this regard, we recommend limiting the potential harms for participants and the burden on the system.

5.3. We recommend using clear, non-stigmatising communication adapted to the (hard-to-reach) target group.

5.4. Integrate a quality monitoring plan that collects necessary data e.g. number of participants, false positives, interval cancers, evolution stage IV lung cancers, etc.

To the Ministers of Welfare and Health and administrations of the federated entities responsible for funding and implementing population screening, to the scientific associations of medical specialists involved in lung cancer screening, and to research institutions

6. For further investigation:

We recommend future re-evaluations if further information becomes available, e.g. from pilot studies, on determining variables such as: participation rate throughout the screening programme, false-positive findings, treatment cost of lung cancer at different stages, approach and impact of incidental findings, introduction of modified screening intervals, etc.



■ REFERENCES

1. World Health Organization (WHO). Screening programmes: a short guide. Increase effectiveness, maximize benefits and minimize harm. Copenhagen: WHO Regional Office for Europe: 2020.
2. Horeweg N, van der Aalst CM, Vliegenthart R, Zhao Y, Xie X, Scholten ET, et al. Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. *Eur Respir J*. 2013;42(6):1659-67.
3. van't Westeinde SC, Horeweg N, De Leyn P, Groen HJ, Lammers JW, Weenink C, et al. Complications following lung surgery in the Dutch-Belgian randomized lung cancer screening trial. *Eur J Cardiothorac Surg*. 2012;42(3):420-9.
4. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. *N Engl J Med*. 2020;382(6):503-13.
5. 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
6. Malhotra J, Malvezzi M, Negri E, La Vecchia C, Boffetta P. Risk factors for lung cancer worldwide. *Eur Respir J*. 2016;48(3):889-902.
7. Gerkens S, Merkur S. Belgium: Health System Review. *Health Syst Transit*. 2020;22(5):1-237.
8. Tabakstop. Op welke financiële tussenkomsten heb je recht? [Web page].2012 [updated 15 January 2024]. Available from: <https://www.tabakstop.be/hoe-stoppen/op-welke-financiële-tussenkomsten-heb-je-recht>
9. Fonds des Affections Respiratoires (FARES). Remboursement des consultations de tabacologie [Web page].2020 [updated 16 February 2022]. Available from: <https://www.fares.be/tabagisme/services-et-missions/vous-etes-un-professionnel/remboursement-des-consultations>



10. Vlaamse Vereniging voor Respiratoire Gezondheidszorg en Tuberculosebestrijding (VRGT). Terugbetaling tabakoloog [Web page].2023. Available from: <https://rookstop.vrgt.be/wat-een-tabakoloog/terugbetaling>
11. Council Recommendation of 9 December 2022 on strengthening prevention through early detection: A new EU approach on cancer screening replacing Council Recommendation 2003/878/EC, O.J. 13 December 2022. Available from: [https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022H1213\(01\)](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022H1213(01))
12. Belgian Health Care Knowledge Centre (KCE). KCE Process book online [Web page].Brussels: KCE;2012. Available from: <https://processbook.kce.be/>
13. Belgian Cancer Registry. Cancer Fact Sheets, Incidence Year 2021. Brussels: 2023.
14. Vrijens F, Verleye L, De Gendt C, Schillemans V, Robays J, Camberlin C, et al. Quality indicators for the management of lung cancer. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2016 04/2016. KCE Reports 266 (266)
15. Neyt M, Devos C, Thiry N, Silversmit G, De Gendt C, Van Damme N, et al. Benefits and costs of innovative oncology drugs in Belgium (2004-2017). Health Technology Assessment (HTA). Brussel: Belgian Health Care Knowledge Centre (KCE). 2021. KCE Reports 343 Available from: <https://doi.org/10.57598/R343C>
16. Pesch B, Kendzia B, Gustavsson P, Jöckel KH, Johnen G, Pohlabeln H, et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer*. 2012;131(5):1210-9.
17. Clinton SK, Giovannucci EL, Hursting SD. The World Cancer Research Fund/American Institute for Cancer Research Third Expert Report on Diet, Nutrition, Physical Activity, and Cancer: Impact and Future Directions. *J Nutr*. 2020;150(4):663-71.
18. European Society for Medical Oncology (ESMO). Thoracic Tumours: Essentials for Clinicians, 2nd edition. 2019.
19. Liao W, Coupland CAC, Burchardt J, Baldwin DR, Gleeson FV, Hippisley-Cox J. Predicting the future risk of lung cancer: development, and internal and external validation of the CanPredict (lung) model in 19.67 million people and evaluation of model performance against seven other risk prediction models. *Lancet Respir Med*. 2023;11(8):685-97.
20. Dobrow MJ, Hagens V, Chafe R, Sullivan T, Rabeneck L. Consolidated principles for screening based on a systematic review and consensus process. *CMAJ*. 2018;190(14):E422-E9.
21. Wise J. NICE advises GPs to offer home tests to all patients with bowel cancer symptoms to reduce waiting lists. *BMJ*. 2023;382:1561.
22. Gram EG, Siersma V, Brodersen JB. Long-term psychosocial consequences of false-positive screening mammography: a cohort study with follow-up of 12-14 years in Denmark. *BMJ Open*. 2023;13(4):e072188.
23. Brodersen J, Siersma VD. Long-term psychosocial consequences of false-positive screening mammography. *Ann Fam Med*. 2013;11(2):106-15.
24. Damhus CS, Quentin JG, Malmqvist J, Siersma V, Brodersen J. Psychosocial consequences of a three-month follow-up after receiving an abnormal lung cancer CT-screening result: A longitudinal survey. *Lung Cancer*. 2021;155:46-52.
25. Marcus PM, Prorok PC, Miller AB, DeVoto EJ, Kramer BS. Conceptualizing overdiagnosis in cancer screening. *J Natl Cancer Inst*. 2015;107(4).
26. Carter SM, Barratt A. What is overdiagnosis and why should we take it seriously in cancer screening? *Public Health Res Pract*. 2017;27(3).



27. Dobbin KK, Ebell M. Should we expect all-cause mortality reductions in large screening studies? *Br J Gen Pract.* 2018;68(671):290-1.
28. Penston J. Should we use total mortality rather than cancer specific mortality to judge cancer screening programmes? Yes. *BMJ.* 2011;343:d6395.
29. DeFrank JT, Barclay C, Sheridan S, Brewer NT, Gilliam M, Moon AM, et al. The psychological harms of screening: the evidence we have versus the evidence we need. *J Gen Intern Med.* 2015;30(2):242-8.
30. Maki KG, Liao K, Lowenstein LM, Lopez-Olivo MA, Volk RJ. Factors Associated With Obtaining Lung Cancer Screening Among Persons Who Smoke. *MDM Policy Pract.* 2021;6(2):23814683211067810.
31. Catalogue of Bias Collaboration OJ, Fanshawe T, Nuan D, . Lead time Bias [Web page].2021 [cited 14 March 2023]. Available from: <https://catalogofbias.org/biases/lead-time-bias/>
32. Gates TJ. Screening for cancer: evaluating the evidence. *Am Fam Physician.* 2001;63(3):513-22.
33. Robert HS, WF. *Clinical Epidemiology: The Essentials.*; 2005.
34. Bonney A, Malouf R, Marchal C, Manners D, Fong KM, Marshall HM, et al. Impact of low-dose computed tomography (LDCT) screening on lung cancer-related mortality. *Cochrane Database Syst Rev.* 2022;8(8):CD013829.
35. Paci E, Puliti D, Lopes Pegna A, Carrozzi L, Picozzi G, Falaschi F, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. *Thorax.* 2017;72(9):825-31.
36. Wille MM, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. *Am J Respir Crit Care Med.* 2016;193(5):542-51.
37. Li M, Zhang L, Charvat H, Callister ME, Sasieni P, Christodoulou E, 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):1491-501.
38. Brodersen J, Voss T, Martiny F, Siersma V, Barratt A, Heleno B. Overdiagnosis of lung cancer with low-dose computed tomography screening: meta-analysis of the randomised clinical trials. *Breathe (Sheff).* 2020;16(1):200013.
39. Jonas DE, Reuland DS, Reddy SM, Nagle M, Clark SD, Weber RP, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. In: *Screening for Lung Cancer With Low-Dose Computed Tomography: An Evidence Review for the U.S. Preventive Services Task Force.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2021.
40. O'Dowd EL, Tietzova I, Bartlett E, Devaraj A, Biederer J, Brambilla M, et al. ERS/ESTS/ESTRO/ESR/ESTI/EFOMP statement on management of incidental findings from low dose CT screening for lung cancer. *Eur Respir J.* 2023;62(4).
41. Nekolla EA, Brix G, Griebel J. Lung Cancer Screening with Low-Dose CT: Radiation Risk and Benefit-Risk Assessment for Different Screening Scenarios. *Diagnostics (Basel).* 2022;12(2).
42. Koninklijk besluit van 13 februari 2020 betreffende de medische blootstellingen en blootstellingen bij niet-medische beeldvorming met medisch-radiologische uitrustingen - Arrêté royal relatif aux expositions médicales et aux expositions à des fins d'imagerie non médicale avec des équipements radiologiques médicaux, B.S. 2020. Available from: https://etaamb.openjustice.be/fr/arrete-royal-du-13-fevrier-2020_n2020200179
43. Centrum voor Kankeropsporing (CvKO). Infosheet belangrijkste indicatoren bevolkingsonderzoeken. 2023.
44. Stichting tegen kanker. Kankerbarometer. 2021.
45. Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers JW, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test



- performance and interval cancers. *Lancet Oncol.* 2014;15(12):1342-50.
46. Yousaf-Khan U, van der Aalst C, de Jong PA, Heuvelmans M, Scholten E, Lammers JW, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. *Thorax.* 2017;72(1):48-56.
47. Baldwin D, O'Dowd E, Tietzova I, Kerpel-Fronius A, Heuvelmans M, Snoeckx A, et al. Developing a Pan-European Technical Standard for a Comprehensive High-quality Lung Cancer CT Screening Program. An ERS Technical Standard. *Eur Respir J.* 2023.
48. 4-IN THE LUNG RUN: towards INdividually tailored INvitations, screening INtervals, and INtegrated co-morbidity reducing strategies in lung cancer screening. [Web page]. European Commission. Available from: <https://cordis.europa.eu/project/id/848294>
49. Tramontano AC, Schrag DL, Malin JK, Miller MC, Weeks JC, Swan JS, 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. *Medical Decision Making.* 2015;35(3):371-87.
50. RIZIV-INAMI. Monitoring Of Reimbursement Significant Expenses - MORSE-report data 2021.
51. Blom EF, Haaf Kt, de Koning HJ. Systematic Review and Meta-Analysis of Community- and Choice-Based Health State Utility Values for Lung Cancer. *PharmacoEconomics.* 2020;38(11):1187-200.
52. Grad R, Légaré F, Bell NR, Dickinson JA, Singh H, Moore AE, et al. Shared decision making in preventive health care: What it is; what it is not. *Can Fam Physician.* 2017;63(9):682-4.
53. Haute Autorité de Santé. Assessment of ethical aspects. 2013.
54. Aghlmandi S, Bhadhuri A. Low-dose CT screening for lung cancer. Basel Institute for Clinical Epidemiology and Statistics; 2022 June.
55. Burzic A, O'Dowd EL, Baldwin DR. The Future of Lung Cancer Screening: Current Challenges and Research Priorities. *Cancer Manag Res.* 2022;14:637-45.
56. Quaife SL, Vrinten C, Ruparel M, Janes SM, Beeken RJ, Waller J, et al. Smokers' interest in a lung cancer screening programme: a national survey in England. *BMC Cancer.* 2018;18(1):497.
57. van der Aalst CM, Ten Haaf K, de Koning HJ. Implementation of lung cancer screening: what are the main issues? *Transl Lung Cancer Res.* 2021;10(2):1050-63.
58. Juth N, Munthe C. The Ethics of Screening in Health Care and Medicine. Springer Dordrecht; 2012.
59. Haute Autorité de Santé. Dépistage du cancer bronchopulmonaire par scanner thoracique faible dose sans injection : Actualisation de l'avis de 2016. Rapport d'orientation. 2021 December.
60. Van Hal G, Diab Garcia P. Lung cancer screening: targeting the hard to reach-a review. *Transl Lung Cancer Res.* 2021;10(5):2309-22.
61. Wiener RS, Koppelman E, Bolton R, Lasser KE, Borrelli B, Au DH, et al. Patient and Clinician Perspectives on Shared Decision-making in Early Adopting Lung Cancer Screening Programs: a Qualitative Study. *J Gen Intern Med.* 2018;33(7):1035-42.
62. Ocak S, Tournoy K, Berghmans T, Demedts I, Durieux R, Janssens A, et al. Lung Cancer in Belgium. *J Thorac Oncol.* 2021;16(10):1610-21.
63. Tomonaga Y, de Nijs K, Bucher HC, de Koning H, Ten Haaf K. Cost-effectiveness of risk-based low-dose computed tomography screening for lung cancer in Switzerland. *Int J Cancer.* 2024;154(4):636-47.
64. Adams SJ, Stone E, Baldwin DR, Vliegenthart R, Lee P, Fintelmann FJ. Lung cancer screening. *Lancet.* 2023;401(10374):390-408.
65. 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. JNCI: Journal of the National Cancer Institute. 2021;113(8):1065-73.
66. 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. Lung Cancer. 2021;159:153-61.
 67. 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. CMAJ open. 2020;8(3):E585-E92.
 68. 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. International journal of nursing studies. 2022;134:104319.
 69. Muratov S, Canelo-Aybar C, Tarride JE, Alonso-Coello P, Dimitrova N, Borisch B, et al. Monitoring and evaluation of breast cancer screening programmes: selecting candidate performance indicators. BMC Cancer. 2020;20(1):795.
 70. O'Dowd EL, Lee RW, Akram AR, Bartlett EC, Bradley SH, Brain K, et al. Defining the road map to a UK national lung cancer screening programme. Lancet Oncol. 2023;24(5):e207-e18.



COLOFON

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Authors:	Fabian Desimpel (KCE), Janis Luyten (KCE), Cécile Camberlin (KCE), Célia Primus-de Jong (KCE), Leen Verleye (KCE), Mattias Neyt (KCE)
Project facilitator:	Els Van Bruystegem (KCE)
Data extraction transformation and loading:	Cindy De Gendt (Cancer Registry Foundation), Julie Verbeeck (Cancer Registry Foundation)
Editorial Synthesis:	Gudrun Briat (KCE)
Reviewers:	Jef Adriaenssens (KCE), Vicky Jespers (KCE), Marijke Eyssen (KCE)
External experts and stakeholders:	Thierry Berghmans (Institut Jules Bordet, Hôpital Universitaire de Bruxelles), Jean-Benoît Burrion (BRUPREV - Centre Bruxelloise de Coordination Pour le Dépistage et la Prévention des cancers), Bernard Carton (Prolong asbl), Sabine Corachan (LUSS - Ligue des Usagers des Services de Santé), Paul De Leyn (UZ Leuven), Michel De Volder (FBHV - Federatie van Brusselse Huisartsen verenigingen), Ingel Demedts (AZ Delta), Brecht Devleesschauwer (Sciensano), Frans Govaerts † (Domus Medica), Leonor Guariguata (Sciensano), Yolande Lievens (Universitair Ziekenhuis Gent, Universiteit Gent), Luigi Moretti (Institut Jules Bordet), Kristiaan Nackaerts (UZ Leuven, Gasthuisberg), Veerle Piessens (Universiteit Gent), Lore Pil (Kom op tegen kanker), Koen Putman (Vrije Universiteit Brussel), Sam Rys (Departement Zorg), Vinciane Sizaire (FARES - Fonds des Affections Respiratoires), Annemiek Snoeckx (UZA - Universitair Ziekenhuis Antwerpen, UA -Universiteit Antwerpen), Stefan Teughels (Domus Medica), Kurt Tournoy (Ugent), Liselot Van De Walle (Department of Health Care), Guido Van Hal (University of Antwerp), Martine Van Hecke (Testaankoop), Koen Van Herck (Cancer Registry Foundation), Jan Van Meerbeeck (UA, UZA), Marc Verheyen (VRGT - Flemish Association for Respiratory Healthcare and Tuberculosis Control)
External validators:	Philippe Autier (i-PRI - International Prevention Research Institute, France), Ingrid Zechmeister-Koss (Austrian Institute for Health Technology Assessment, Austria), Dirk De Ruyscher (Maastr, Netherlands)
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