Lung cancer screening in a high-risk population

a fight worth fighting?

All.Can Belgium

Changing cancer care together

About All.Can Belgium

All.Can Belgium is a dynamic multi-stakeholder platform that unites the Belgian cancer care community to make tangible progress in cancer patient care. With the ambition to achieve sustainable, efficient and patient-centered cancer care, All.Can Belgium brings together a wide range of stakeholders, including patient and care representatives, health professionals, health experts, policy makers and industry representatives.

Our mission is clear: improve cancer care by combining sustainability, accessibility and patient-centeredness and placing them high on the policy agenda. By identifying and reducing waste in care, using resources more efficiently, and addressing unmet medical needs, we strive to improve patient outcomes. Innovation plays a crucial role here to improve both efficiency and quality of care.

All.Can Belgium has **five key priorities**:

1. Uniting stakeholders around a shared vision for cancer care.
2. Initiating and realizing projects to achieve this vision.
3. Proposing solutions for more efficient and innovative care.
4. Proactive participation in policy debate.
5. Creating public support for the vision of better cancer care.

Together we are committed to stronger and more future-proof cancer care throughout the entire care continuum.

Lung Cancer Working Group

The Lung Cancer Working Group is an initiative of All.Can Belgium with a mission to help improve efficiency in lung cancer care.

Although lung cancer represents 13% of the total number of cancer cases in Belgium, there is a lack of support for lung cancer patients compared to other types of cancer like breast cancer. There is a need for more efficiency along the pathway to improve outcomes, such as lung cancer screening, prevention, and patient support.

By leveraging the collaboration between the different stakeholders our Lung Cancer Working Group aims to address those areas where patient needs are the highest.

All.Can Belgium — Changing cancer care together

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Executive summary

Lung cancer continues to be the most common cause of cancer-related death, accounting for about 375,000 deaths across Europe in 2022.

The most important factor determining the dismal prognosis of lung cancer is that this tumor type is generally diagnosed in an advanced stage, when curative treatments are no longer an option. Theoretically, a targeted lung cancer screening program could increase the rate of patients that are diagnosed in an early disease stage allowing a surgical treatment. This would have a major impact on the lung cancer-related mortality.

Over the years, several randomized controlled trials (RCTs) and meta-analyses have provided convincing evidence showing that low-dose computed tomography (LDCT) lung cancer screening in a high-risk population results in a significant reduction in lung-cancer related death and a clear shift towards lower lung cancer stages at diagnosis. However, as this lung cancer screening is offered to asymptomatic individuals, it is important to ensure that the benefits of screening outweigh the possible risks. In the context of LDCT lung cancer screening, the most cited potential risks consist of radiation exposure from the scan, misdiagnosis due to a false positive result and overdiagnosis. Due to a combination of perceived uncertainty on the potential benefits and harms of lung cancer screening, practical hurdles and financial concerns, the list of countries who implemented an organized, national LDCT lung cancer screening program continues to be short.

Through a series of interviews, questionnaires and face-to-face discussions involving a broad range of stakeholders, All.Can Belgium evaluated the enthusiasm for and the feasibility of a national LDCT lung cancer screening project in Belgium. Based on the information gained from these different interactions, All.Can Belgium formulated the following **recommendations**. >>>

Methodology

As a basis for this white paper, All.Can Belgium distributed a questionnaire among a wide range of individuals, societies, and organizations with a potential stake in the development of a lung cancer screening program in Belgium. This questionnaire was followed up by a series of interviews with the responding stakeholders for a more in-depth discussion on the potential advantages and challenges associated with lung cancer screening. The initial version of the white paper you are about to read was a blend of the available scientific literature on the topic of lung cancer screening and the key take aways from these interviews. This first draft of the paper was subsequently discussed during a round table debate, bringing together a selection of relevant stakeholders. The insights and thoughts that were shared during this round table debate were subsequently used to finalize the white paper. As such, it is important to underscore that the stakeholders who were consulted for this white paper did not co-author the paper and therefore do not necessarily agree with its content. A full list of the stakeholders that were consulted can be found as an addendum to the paper.

1. LDCT lung cancer screening can save lives. As such, setting up a lung cancer screening program is a fight worth fighting.

2. Not investing in a structured lung cancer screening program will form the basis for ad hoc screening initiatives that lack standardization and quality control.

3. Lung cancer screening should ideally be organized through a network of expertise centers, assuring adequate quality control along the entire screening process and subsequent investigations.

4. The first line of care will have to play an important role in setting up a lung cancer screening program. As such, GPs, pharmacists, and all other components of this first line of care need to be closely involved .

5. To increase the enthusiasm for lung cancer screening among the first line of care there is a need for balanced educational material clearly discussing the potential benefits and harms of lung cancer screening.

6. There is a need for more education on lung cancer among the general population. By emphasizing the multifactorial nature of lung cancer, the smoking stigma can be reduced. Furthermore, by underscoring the curative options for early-stage lung cancer, you can eradicate the misconception that lung cancer is an immediate death sentence.

7. A lung cancer screening program should always be flanked by a structured smoking cessation program. In doing so, the screening will become a teachable moment on the possibilities of smoking cessation.

8. The success of a screening program is highly dependent on the existence of high-quality care pathways.

9. A cost-effectiveness study indicates that lung cancer screening can be cost-effective if the policymaker's willingness to pay ranges between €20 000 and €30 000 per QALY gained. The government now needs to decide if they are willing to make this investment.

10. Implementation studies for lung cancer screening are warranted and will generate a wealth of data on the efficacy, feasibility, and participation rate.

A brief introduction to lung cancer

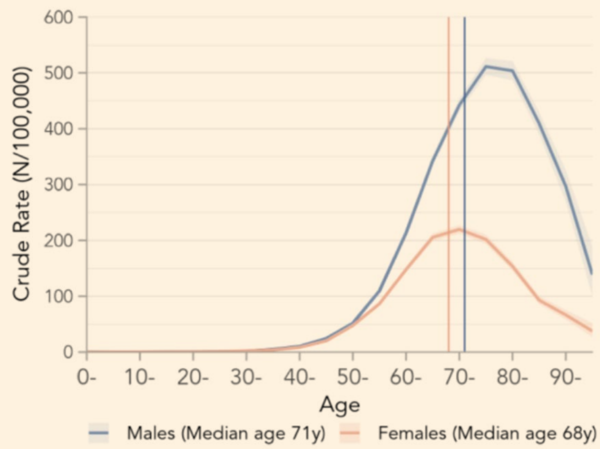
Epidemiology

According to GLOBOCAN data, lung cancer was the second most common cancer among European males in 2022, while it ranked third among women. In both sexes, lung cancer continues to be the most common cause of cancer-related mortality, accounting for about 375,000 deaths across Europe in 2022.[1] The most recent data from the Belgian Cancer Registry indicate 9,410 new lung cancer diagnoses in 2022. In addition to its high incidence, lung cancer comes with staggering mortality numbers.[2] In 2021, on average 16 people a day died from lung cancer in Belgium. In 2021, lung cancer proved to be the third and second most important cause of premature death among Belgian men (after suicide and COVID-19) and women (after breast cancer), respectively.[3]

Historically, lung cancer came with a male predominance. Over the last decades, however, we have witnessed an increasing incidence among women (average annual percentage change of +3.8%), while the incidence gradually decreased in men (average annual percentage change of -1.3%).[4] As a result of this evolution, the Belgian lung cancer incidence rates for men and women are gradually converging, with a total of 5,800 (59.8%) new diagnoses in males and 3,894 (40.2%) in women in 2022.[4] Of note, this increasing incidence of lung cancer in women is not limited to Belgium, but has been observed in many high-income countries around the globe.[5,6,7] Recently published cancer mortality predictions even show that in 2023, lung cancer has surpassed breast cancer as the leading cause of cancer-related death in women.[8]

The incidence of lung cancer is strongly associated with age. Data from the Belgian Cancer registry indicate a rising incidence from 45 years onwards, peaking at 70-75 years after which the incidence decreases rapidly in the oldest age groups **(Figure 1)**.

Figure 1 Age-specific incidence rate of lung cancer by sex between 2018 and 2022 (data provided by the Belgian Cancer Registry [BCR]. Reproduced with permission).[4]



Prognosis

As indicated earlier, lung cancer comes with a dismal prognosis. According to the Belgian Cancer Registry, the 5-year net survival of Belgian lung cancer patients between 2018 and 2022 was 26% for men and 34% for women.[4] This analysis also revealed a strong inverse relationship between age and survival in lung cancer, with 5-year relative survival rates ranging from 35% to 46.1% in patients aged 15-49 years as compared to 21% to 28% in the subgroup of patients above 65 years of age.[4] However, the most determining factor in the prognosis for patients with lung cancer consists of the disease stage at diagnosis. The latter is amply illustrated by the 5-year overall survival (OS) data across the different lung cancer stages in the recently published 9th edition of the TNM staging for lung cancer **(Figure 2)**. While patients with a small, localized lung tumor (stage IA disease) were found to have a 5-year OS rate of 82%, this drops to 21-44% in patients with locally advanced disease (stage III) and just 7-18% for patients with metastatic lung cancer (stage IV).[9]

These survival data clearly underscore the importance of an early diagnosis in patients with lung cancer. Unfortunately, early signs of lung cancer such as chronic cough, or shortness of breath are often vague and difficult to recognize as lung cancer symptoms. As a result, the majority of patients only gets a diagnosis when the disease has already spread to other parts of the body (stage III or IV disease). In fact, according to the Belgian Cancer Registry, 48% of patients diagnosed with lung cancer in 2022 had stage IV disease, precluding a curative treatment strategy.[4] This high rate of stage IV disease at diagnosis stands in sharp contrast with what is observed in other common cancer types such as breast, prostate or colorectal cancer, where only 7%, 13.7% and 21% of patients have stage IV disease at the time of the initial diagnosis, respectively.[10,11,12] This late diagnosis of lung cancer is therefore one of the major contributors to the poor prognosis of this disease relative to other cancer types.

"48% of patients diagnosed with lung cancer in 2022 had stage IV disease."

A targeted lung cancer screening program could increase the rate of patients that are diagnosed in an early disease stage allowing a surgical treatment. This would have a major impact on the lung cancer-related mortality.

Figure 2 Survival by clinical stage according to the 9th TNM edition for lung cancer.[9]

Stage	Median OS (months, 95%CI)	5-year OS rate (%, 95%CI)
IA	Not reached	82% (82, 83)
IB	9 (8.4, .)	69% (67, 70)
IIA	8 (7.2, .)	62% (60, 64)
IIB	5.8 (5.5, 6.3)	54% (53, 56)
IIIA	4 (3.7, 4.2)	44% (42, 46)
IIIB	2.1 (1.9, 2.4)	32% (28, 34)
IIIC	1.3 (1.1, 1.4)	21% (16, 25)
IVA	1.3 (1.3, 1.4)	18% (16, 19)
IVB	0.7 (0.7, 0.8)	7% (6, 8)

Risk factors

Several risk factors, modifiable or not, are known to increase the risk for lung cancer. In fact, data from the UK reported in 2018 indicate that almost 4 out of 5 lung cancers are preventable.[13] Already in the 1950s it was established that smoking was significantly associated with the development of lung cancer.[14,15] Worldwide it is estimated that about 90% of lung cancer cases among men and over 80% of cases in women are attributable to tobacco use.[16] While the association between smoking and lung cancer is clear, it is important to underscore that still about 15% of all lung cancer patients are never smokers and the proportion of never smokers among lung cancer patients is gradually increasing. Of note, this trend is even more pronounced in Asia. In this respect, other factors such as occupational exposures (e.g., asbestos, radiation, heavy metals), air pollution, genetic susceptibility, or a poor diet, may act independently or in concert with tobacco smoking as predisposing factors for lung cancer.[16] In addition to this, also a history of other pulmonary illnesses, such as chronic obstructive pulmonary disease (COPD), tuberculosis, emphysema or chronic bronchitis increase the risk for lung cancer.[17,18]

"Tobacco use continues to be the main contributor to lung cancer."

As tobacco use continues to be the main contributor to lung cancer, it is interesting to zoom in on the smoking prevalence in Belgium. According to data generated by the Belgian Health Interview Survey (BHIS) in 2018, about a fifth of the Belgian population (19.4%) above the age of 15 was an active smoker. Of them 15.4% were daily smokers, while the remaining 4% indicated to be an occasional smoker. In addition to this, 23.1% indicated to be a former smoker. The daily smoking prevalence was highest in the Walloon Region at 18.8% followed by the Brussels Capital Region (16.5%) and the Flemish Region (13.3%). Importantly, the prevalence of smoking gradually decreased over time from 30.3% in 1997 to 23.0% in 2013 and 19.4% in 2018. In parallel, the percentage of never smokers increased from 40.7% in 2001 to 57.5% in 2018. The prevalence of smoking was higher among men than women with rates of 24.5% and 14.6%, respectively, in 2018. In addition, the prevalence of daily smoking proved to be markedly lower in people with a higher education (10.1%) compared to lower levels of education. Finally, the percentage of heavy smokers, defined as $\geq$20 cigarettes/day, was reported at about 10% in 2004 after which it slowly decreased to 6.5% in 2013 and 4.7% in 2018.[19] A logical contributor to the drop in tobacco use over the last decades consists of the anti-tobacco legislation that was introduced during this timeframe. To give some examples: a ban was imposed on advertisement for tobacco products, laws were voted prohibiting smoking in restaurants, bars, and at the workplace, and health warnings on packaging of tobacco products became mandatory. Despite investment from the government to stimulate smoking cessation and in campaigns to discourage smoking, we should expect more incentives from the authorities if we want to work towards a smoke-free generation in the near future!

"It is to be expected that also e-cigarettes represent a risk factor for lung cancer."

Unfortunately, the gradual drop in smoking prevalence over time has been paralleled by an increasing uptake of nicotine-laden vapes, or e-cigarettes. As these e-cigarettes do not burn tobacco, one may assume that vaping e-liquid is less harmful than inhaling cigarette smoke. In recent years, however, accumulating data are showing that the toxic effects of e-cigarette aerosol exposure are essentially identical to that caused by combustible cigarette smoking.[20]

While the actual impact of these toxic effects on the development of lung cancer is yet to be determined, it is to be expected that also e-cigarettes represent a risk factor for lung cancer. In line with this, data reported during the 2024 annual meeting of the American Thoracic Society indicate that former smokers who shift to e-cigarettes rather than stop nicotine intake altogether, continue to face a higher risk of developing lung cancer and to die from the disease.[21] Importantly, data from a survey conducted by Kom Op Tegen Kanker show that half of the adolescents between 12 and 26 year who vape are also smoking tobacco. Furthermore, half of the respondents to this survey indicate that for them vaping was a steppingstone to start tobacco use.

Societal burden

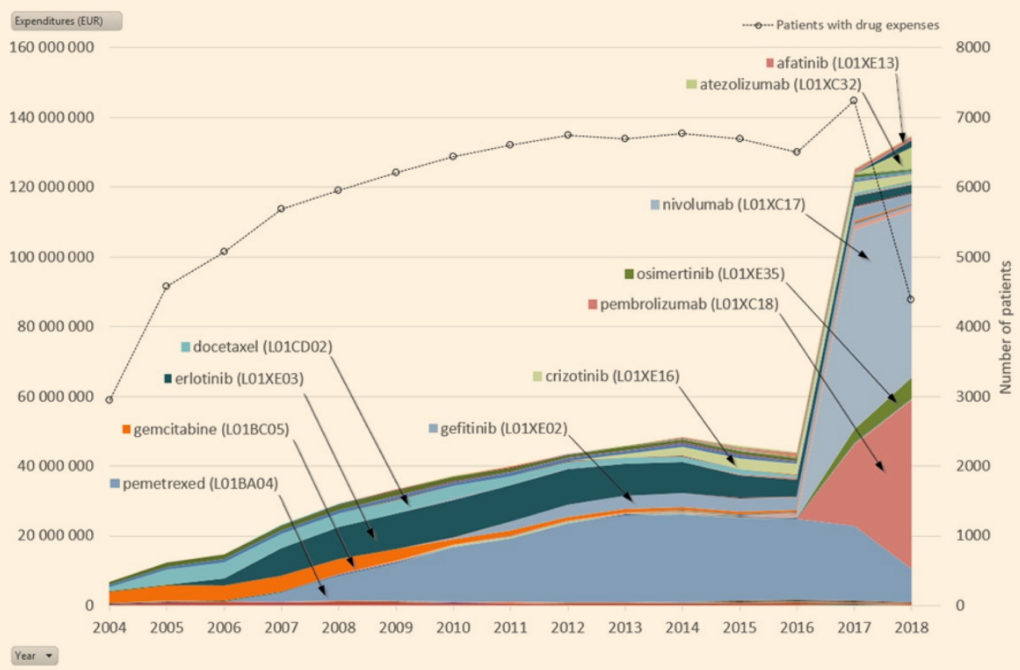
Lung cancer is not only a major health problem for individual patients, but also comes with an enormous societal burden. In 2019, the direct and indirect cost of lung cancer in Belgium was estimated at a striking 9 billion Eur.[22] A main contributor to this societal price tag consists of the cost for drugs that are used in patients with advanced NSCLC.

"The cost of lung cancer in Belgium was estimated at a striking 9 billion euro."

In this respect, data from the Belgian Health Care Knowledge Centre (KCE) show an explosion in the drug expenditures for lung cancer patients from 2015 onwards (Figure 3).[23] A detection of lung cancer in an earlier disease stage would significantly decrease the need for these expensive drugs, bringing some alleviation to the stretched healthcare budget in our country. Very recently, clinical trials have demonstrated a clinical benefit of immunotherapy and targeted agents in the (neo)adjuvant treatment for patients with early-stage, resectable non-small cell lung cancer (NSCLC). The introduction of these options in clinical practice will somewhat dilute the financial impact of earlier lung cancer detection. However, these (neo)adjuvant therapies are not in use for patients with stage I disease, the detection of which is the main objective of lung cancer screening.

In addition to the direct costs, associated with the management and treatment of patients, lung cancer also comes with important indirect costs, related to productivity loss and informal care. In fact, many patients with lung cancer stop working when they are diagnosed and a lot of them never make it back to the work floor. As a result, lung cancer was found to be responsible for a quarter (23%) of the productivity loss due to cancer-related mortality in Europe, corresponding to a total cost of 17.5 billion Eur.[24]

Figure 3 oncological drug expenditures for NSCLC per calendar year. Importantly, the net expenditures in this figure equal the gross expenditures minus the patient copayments. As such, discounts related to managed entry agreements are not taken into consideration (data provided by the Belgian Health Care Knowledge Centre [KCE]. Reproduced with permission).[23]



A brief introduction to cancer screening

According to the WHO, screening is defined as the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population.[25] Specifically in the context of cancer, screening can help to identify a malignant tumour at an early stage, when the disease is still curable, ultimately leading to an improved survival. Population-based screening is a complex undertaking and various aspects should be considered before it can be implemented. In this respect, Dobrow et al. have formulated **12 overarching principles** for a successful screening program:[26]

1. The epidemiology of the disease or condition should be adequately understood, and the disease or condition should be an important health problem.
2. The natural history of the disease or condition should be adequately understood, the disease or condition is well-defined, and there should be a detectable preclinical phase.
3. The target population for screening should be clearly defined (e.g., with an appropriate target age range), identifiable and able to be reached.
4. Screening test performance characteristics should be appropriate for the purpose, with all key components specific to the test (rather than the screening program) being accurate (e.g., in terms of sensitivity, specificity and positive predictive value), reliable and reproducible. The test should be acceptable to the target population, and it should be possible to perform or administer it safely, affordably, and efficiently.
5. The screening test result should be clearly interpretable allowing the identification of screening participants who should/should not be offered further diagnostic testing and other post-screening care.
6. There should be an agreed course of action for screening participants with a positive screening test results that involves diagnostic testing, treatment or intervention, and follow-up care that will modify the natural history and clinical pathway for the disease or condition. This care path should be available, accessible, and acceptable to those affected and should result in improved outcomes. The burden of testing on all participants should be understood and acceptable, and the effect of false positive and false negative tests should be minimal.
7. There should be adequate existing infrastructure (e.g., financial resources, human resources, information technology, facilities, equipment, and test technology), or a clear plan to develop adequate infrastructure, that is appropriate to the setting to allow for timely access to all components of the screening program.
8. All components of the screening program should be coordinated and, whenever possible, be integrated into a broader health care system (including a formal system to inform, counsel, refer and manage the treatment of screening participants) to optimize care continuity and ensure no screening participant is neglected.
9. All components of the screening program should be clinically, socially, and ethically acceptable to screening participants, health professionals and society. There should be effective methods for providing screening participants with informed choice, promoting their autonomy, and protecting their rights.

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

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

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

A screening test may lead to **4 different results**. The majority of people will have no disease and have a negative test. For these '**true negative**' patients, the impact of the screening is limited to the discomfort of the test and perhaps a short period of fear while awaiting the results. If the screening test consists of an X-ray or CT-scan, the radiation dose and the associated risks are an additional disadvantage. In a well-designed screening program, most people who have the disease will be picked up by the screening test. This **true positive** population in which lung cancer is diagnosed in an early stage are the ones who clearly benefit from a screening program, as the earlier detection of the disease usually leads to a better prognosis. However, a proportion of patients who test positive on the screening test may ultimately turn out not to have the disease. Such a **false positive** result has a detrimental effect on patients as it induces fear and the discomfort and risks of additional tests (e.g., biopsy, repeated scans, etc.). Finally, the screening test may also fail to pick up the disease in a proportion of patients. These **false negatives** clearly do not benefit from the screening program and may even be harmed because of the false reassurance the screening test gives them. In order for a screening program to be successful it is self-evident that the proportion of false negatives and false positives needs to be as low as possible.

Apart from the four possible test results above, screening procedures may also reveal the presence of other diseases, or abnormalities that are unrelated to the disease for which the screening program was set up. These so-called **incidental findings** may provide an additional advantage if they lead to an earlier treatment and a better outcome. However, minor, or clinically insignificant incidental findings or pathological entities for which no effective therapies are available may also lead to unnecessary investigations, additional costs, and patient anxiety. Specifically in the context of cancer, screening can also lead to an '**overdiagnosis**' of incidental cancers that may very well never have caused harm. This overdiagnosis may unnecessarily label people as cancer patients, leading to unnecessary overtreatment and associated toxicity, a detriment in quality of life due to anxiety and potential financial, or social distress. When implementing a screening program, it is therefore also important to formulate a strategy on how to deal with incidental findings and to minimize the rate of overdiagnosis.

Low-dose Computed Tomography lung cancer screening: clinical trial results

Over the years, several, large-scale randomized controlled trials (RCTs) in the US and Europe have evaluated the effectiveness of a low-dose Computed Tomography (LDCT) lung cancer screening.

The most commonly cited of these RCTs consist of the National Lung Screening Trial (NLST) performed in the US and the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON), which ran in Belgium and the Netherlands.[27,28]

The **NLST trial** was initiated in 2002 and recruited a total of 53,454 participants. People in this trial were aged 55–74 years and were either current smokers, or former smokers with a smoking history of at least 30-pack-years. Participants in this trial were randomized into either a LDCT or chest X-ray screening group and underwent annual screening over 3 years. Interestingly, this trial reported an overall 20% ($p = 0.004$) reduction in lung cancer-specific mortality after 6.5-years of follow-up when using LDCT as compared to chest X-ray for LCS. In addition to this, NLST also demonstrated a significant reduction in all-cause mortality with LDCT compared to X-ray after 6.5 years, with an incidence rate ratio (IRR) of 0.93 (95%CI: 0.88-0.99) after 6.5 years. This marks NLST as the only cancer screening trial for a single cancer type that was able to show a significant reduction in all-cause mortality. However, it must be noted that the effect on overall mortality is decreasing with longer follow-up.[29]

In contrast to NLST, the **NELSON trial** compared LDCT screening at baseline and after 1,3 and 5.5 years to no screening at all. The study was initiated in 2003 and included a total of 15,792 people. The target population in NELSON differed from that of NLST with an age interval of 50–74 years. Both smokers and former smokers with a history of ≥30 pack-years were included. The final NELSON results with a follow-up of 10 years were presented in 2020, showing a cumulative rate ratio for lung cancer death of 0.76 (95%CI: 0.61–0.94; p= 0.01).[28]

In 2022 a systematic review and meta-analysis was published, including 11 RCTs of lung cancer screening using LDCT and reporting mortality or harm outcomes. Overall, almost 95.000 patients were included in this analysis.[30] When combining the data from 8 clinical studies for which all-cause mortality data were available, the analysis showed a significant reduction of 5% in all-cause mortality (RR[95%CI]: 0.95[0.91-0.99]) with LDCT screening. According to these data, 210 people would need to be screened to prevent one death from all-cause mortality. In terms of lung cancer-specific mortality, the meta-analysis revealed a 21% benefit with LDCT screening (RR[95%CI]: 0.79[0.72-0.87]) **(Figure 4)**, with a number needed to screen (NNS) to prevent one additional lung cancer-related death of 296. Of note, these figures compare favorably to the NNS for cervical, breast and colorectal cancer screening in Flanders.[31,32,33]

Very recently, an analysis of the impact of lung cancer screening among patients in the US Veterans Health administration (N= 57.919) further solidified the findings of this meta-analysis indicating a significantly better 5-year overall and lung cancer specific survival among patients who were diagnosed as compared to those who were not. In this trial, the improvements in all-cause and lung-cancer specific survival were reported at 21% (95%CI: 0.67-0.92, p= 0.003) and 39% (95%CI: 0.50-0.74; p< 0.001).(34)

In addition to evaluating the effect of LDCT lung cancer screening on mortality, the previously mentioned meta-analysis also assessed whether screening led to a ‘stage shift’ in the diagnosis of lung cancer (i.e., a higher proportion of patients being diagnosed in an earlier, curative disease stage). After 1 year of follow-up, LDCT lung cancer screening reduced the incidence of stage IV lung cancer diagnoses by

52% (RR[95%CI]: 0.48[0.30-0.77]). After 10 years of follow-up, the difference in the incidence of stage IV diagnoses remained significant, with 23% less stage IV lung cancers in the LDCT group (RR[95%CI]: 0.77[0.69-0.86]).[30] In line with this finding, the recently published analysis of the US Veterans Health administration indicated a significantly higher rate of stage I lung cancer diagnoses among patients who underwent lung cancer screening compared to those who did not (52% vs. 27%; p< 0.0001).[34]

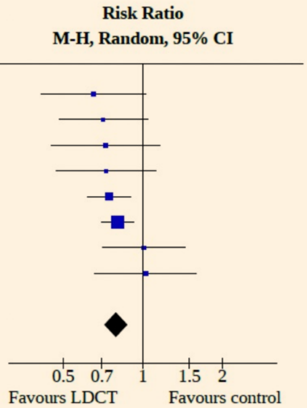
As discussed before, an effective screening program should be able to minimize the number of false positive and false negative findings. In this respect, the meta-analysis discussed above indicates a very wide range of false positivity rates across the different studies, ranging from 8% to 46% in the first screening round. However, this false positivity rate decreased in subsequent screening rounds.[30] When defining a false positive result as the detection of an indeterminate or suspicious lung nodule which eventually did not turn out to be malignant, the NLST and NELSON studies came with a false positivity rate during the first screening round of 27% and 7%, respectively.[27,28] Lung cancer screening with LDCT results in invasive procedures for false positive findings in 0.1%–1.7% of the participants invited for screening, with few trials reporting complications of these procedures.[30] The incidence of false negatives across the different clinical studies was low, with a negative predictive value of 97.7-99.9%.[35]

"After 1 year of follow-up, LDCT lung cancer screening reduced the incidence of stage IV lung cancer diagnoses by 52%."

Figure 4 Meta-analysis of lung cancer-related mortality with LDCT screening (reproduced with permission from Bonney et al.).[30]

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Field 2021	30	1987	46	1981	4.2%	0.65 [0.41 , 1.03]
Paci 2017	43	1613	60	1593	5.9%	0.71 [0.48 , 1.04]
Becker 2020	29	2029	40	2023	3.9%	0.72 [0.45 , 1.16]
Pastorino 2012	40	2376	40	1723	4.7%	0.73 [0.47 , 1.12]
De Koning 2020	181	7900	242	7889	24.3%	0.75 [0.62 , 0.90]
Aberle 2011	356	26722	443	26732	45.7%	0.80 [0.70 , 0.92]
Infante 2015	59	1264	55	1186	6.8%	1.01 [0.70 , 1.44]
Wille 2016	39	2052	38	2052	4.5%	1.03 [0.66 , 1.60]
Total (95% CI)		**45943**		**45179**	**100.0%**	**0.79 [0.72 , 0.87]**
Total events:	777		964			

Heterogeneity: Tau² = 0.00; Chi² = 4.79, df = 7 (P = 0.69); I² = 0%
Test for overall effect: Z = 4.92 (P < 0.00001)
Test for subgroup differences: Not applicable



Potential harms of LDCT lung cancer screening

By definition, screening is offered to asymptomatic individuals. As such, it is important to ensure that the benefits of screening outweigh the possible risks.

In the context of LDCT lung cancer screening, the main risks consist of radiation exposure from the scan, misdiagnosis due to a false positive result and overdiagnosis.

With respect to radiation exposure, cumulative evidence from randomized clinical trials has shown that LDCT screening carries a negligible risk of radiation exposure.[36] In fact, since the first lung cancer screening trials were performed, technical improvements of hardware and software have resulted in a reduction of effective radiation dose.[37] A recently published technical standard for lung cancer screening developed by the European Respiratory Society (ERS) recommends to keep the volume of CT dose index as low as possible with an effective radiation dose well below 2 mSv.[38] As a means of comparison, the estimated average exposure to ionizing radiation in Belgium is 4 mSv per year, of which an estimated 2.4 mSv per year comes from natural radiation sources.[39] In other words, the effective radiation dose that comes from of a single LDCT screening round is lower than ambient annual background radiation.

The German Federal Office for Radiation Protection published conservative estimates of the lifetime attributable cancer risks as a result of from repeated LDCT screening tests for a German population of heavy smokers or ex-smokers. Taking into account a yearly screening of (former) smokers aged between 50 and 75 years, the estimated radiation-related lifetime attributable risk to develop cancer was calculated at 0.25% for women and about 0.1% for men.[40] Given the fact that LDCT lung cancer screening is associated with a 20% reduction in cancer-related mortality, the benefit of screening markedly outweighs the radiation risk, especially given the low dose CT that is used for this screening process.

When using high quality standards, LDCT lung cancer screening does not lead to a high number of false-positive results, leave alone an excessive number of subsequent unnecessary procedures or treatments (invasive procedures for false positive findings were reported at 0.1%–1.7%).[30] Nevertheless, false positive results may still have psychosocial consequences. To mitigate this, it is very important to rapidly perform follow-up diagnostics to rule out lung cancer as soon as possible. In addition to this, the screening program should ideally be flanked by an easily accessible psychological support structure for participants with a (false) positive test result.

"Given the fact that LDCT lung cancer screening is associated with a 20% reduction in cancer-related mortality, the benefit of screening markedly outweighs the radiation risk, especially given the low dose CT that is used for this screening process."

Overdiagnosis in cancer screening relates to the detection of an indolent pathology that would not otherwise have become clinically apparent. To avoid overtreatment and its potential morbidity, mortality, and associated treatment costs it is important to reduce the rate of overdiagnosis during lung cancer screening.

"We have to accept that there will always be some overdiagnosis when implementing a lung cancer screening program. However, this is also the case with screening for breast cancer, or colorectal cancer."

Data on the incidence of overdiagnosis in LDCT lung cancer screening trials vary significantly, from 0% to more than 60%.[35] In a meta-analysis comparing LDCT screening to no screening, the estimated rate of overdiagnosis proved to be relatively low, at 18%.[30] Over the years, several potential strategies have been developed to reduce overdiagnosis rates in LDCT lung cancer screening programs. This includes the use of risk models that can distinguish high-risk nodules from low-risk nodules (e.g., using radiomics, or artificial intelligence) and using models to quantify the volume doubling time of nodules.[41,42,43,44] Another option is to apply a longer interval between screening rounds (i.e., less screening rounds, means less false positives and less overdiagnosis).[43,45] However, increasing the time between screening rounds will of course also have an impact on the efficacy of the screening program.

Probably the most feasible strategy to minimize overdiagnosis in clinical practice is the adherence to a conservative management of nodules with a clear and standardized protocol for referral. This includes a stringent definition of a positive, negative, and indeterminate screening result. To allow for a better standardization, it is probably best to centralize the reading of the LDCT scans. Of note, a similar centralized approach is also used for breast cancer screening in the Netherlands. Nevertheless, we have to accept that there will always be some overdiagnosis when implementing a lung cancer screening program. However, this is also the case with screening for breast cancer, or colorectal cancer. As such, it would not be wise to hold the potential for overdiagnosis as an argument to abandon the idea of LDCT lung cancer screening.

Implementing LDCT lung cancer screening in Belgium

As discussed above, the RCT evidence supporting LDCT lung cancer screening in a high-risk population is irrefutable, with a reduction of about 20% in the lung-cancer related death and a clear shift towards lower lung cancer stages at diagnosis. Notwithstanding these convincing evidence, the list of countries who implemented an organized, national LDCT lung cancer screening program is limited. In Europe, a national screening program is already in place in Croatia, the Czech Republic, Poland, and the United Kingdom, with ongoing implementation studies in Italy and regional feasibility studies in France. Nevertheless, more than a decade of feasibility and pilot studies around the globe has yielded a wealth of information that can guide countries to successfully implement a national screening program.

1. Select the right target population

The success of a targeted LDCT lung cancer screening largely depends on the ability to identify the population that has the highest risk to develop lung cancer and who are most likely to benefit from screening. A clear delineation of the target population is essential to maximise the cost-effectiveness ratio of the screening. Unfortunately, we currently don't have biomarkers to facilitate a stringent selection of the target population. Given the association of lung cancer with age and smoking history, these two criteria were traditionally used to delineate the target population in the different RCTs. In this respect, data suggest that 45-60% of incidental lung cancers would be captured if the target population is restricted to:[46]

- ✅ Males between 50 and 74 years of age, females between 55 and 80 years of age
- ✅ Current heavy smokers (>20-30 packyears), or former heavy smoker who stopped smoking within the last 10 years.

An important hurdle that is associated with these criteria lies in the fact that there is no centralized database, or registry in Belgium on the smoking habits, or detailed history of the population. To overcome this, several initiatives use a multistep approach in which an initial invitation is sent based on the age of the potential participant, after which a structured questionnaire is used to determine his/her smoking history. However, in such a system you strongly rely on feedback from the potential participant. Especially when it comes to smoking, people tend to downplay their smoking pattern, while other may exaggerate their smoking history to be allowed to be screened.

Importantly, also the fitness of people needs to be taken into consideration when thinking about the target population for lung cancer screening. In fact, if the screening leads to the detection of a lung cancer but the patient is not fit enough to undergo the necessary treatment for this lung cancer, nothing is gained from the screening. In addition, also the bodyweight of people may be of relevance. In fact, obesity may impact the image quality of LDCT, which in turn has an effect on the efficacy of the lung cancer screening.[47,48]

In addition to smoking history and age, several other factors such as occupational exposures (e.g., asbestos, radiation, heavy metals), air pollution, or genetic susceptibility also increase the risk for lung cancer. These risk factors are not accounted for in the current screening criteria, which in part explains why half of the incidental lung cancers will be missed. In this respect, it is important to underscore that many oncogene-driven NSCLCs (e.g., EGFR mutant, ALK rearrangements) occur in non-smokers and tend to affect younger individuals. To address this issue, several risk prediction models have been developed. For example, the Liverpool Lung Project (LLP) model includes age, sex, smoking duration, personal and family history of cancer, personal history of pneumonia, and asbestos exposure as risk factors. In contrast, the PLCOM2012 model examines age, race, education, body mass index, chronic obstructive pulmonary disease (COPD), personal and family history of cancer, smoking status, duration and intensity of smoking, and years since cessation of smoking as additional risk factors. With respect to the latter, data have shown a higher sensitivity and a better positive predictive value for the detection of lung cancer when the PLCOM2012 model is used to select the target population for LDCT lung cancer screening instead of the criteria used in the NLST trial.[49] However, while these models are able to better define a high-risk population for lung cancer, their complexity might hamper their widescale use in clinical practice.

2. Couple lung cancer screening with smoking cessation

An often-heard argument against lung cancer is that it is better to focus on smoking prevention and cessation instead of investing in screening. Indeed, tobacco cessation remains the most important intervention to decrease lung cancer risk, even among long-term or older smokers. In addition, smoking cessation will also reduce premature mortality due to cardiovascular disease and cerebral disease and improve the overall health of smokers.[50] For the moment, however, the reimbursement of nicotine replacement therapy is not universal in Belgium and the motivation for smokers to consult a tobacologist is low. Furthermore, putting all your eggs in the smoking cessation basket also comes with some other hurdles. For example, the smoking prevalence in Belgium stagnates despite increasing restrictions and a continuous increase in taxes on tobacco products.

In addition to this, a resulting decrease in lung cancer mortality from smoking cessation efforts only becomes apparent after about 20 years, which does not alleviate the immediate situation. Furthermore, recently published data from the Netherlands indicate that smoking cessation interventions may not effectively substitute lung cancer screening to combat lung cancer death and prolong life in a lung cancer screening-eligible population.[51]

Allowing current smokers to participate in lung cancer screening has been a long-standing subject of debate. In fact, there is an argument to make that screening is not useful in people who continue to increase their risk and that lung cancer screening in fact gives smokers a 'license to smoke'. However, by excluding current smokers, the screening program will inevitably miss the majority of lung cancers. Instead, we should consider lung cancer screening an opportunity to discuss tobacco cessation in high-risk smokers.

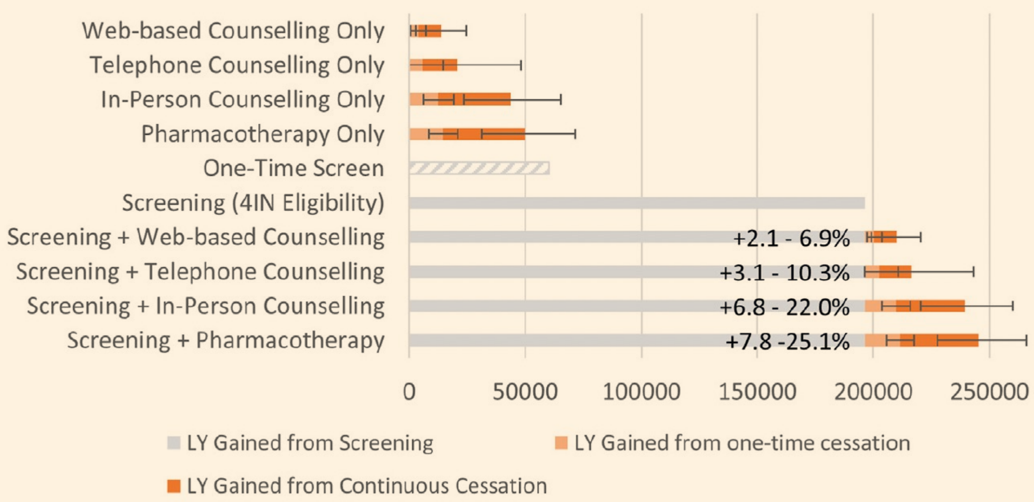
While the research regarding smoking cessation in the context of lung cancer screening is scarce, the available data indicate that many smokers undergoing lung cancer screening are motivated to quit and are interested in receiving cessation care.[52,53] These studies show a higher motivation to quit smoking and a higher cessation rate among screening participants compared to the general population. In addition to this, a positive or indeterminate screening result seems to prompt cessation and decrease the smoking relapse rate.[54]

While the impact of comprehensive cessation support to lung cancer screening participants is not well studied, the available data do suggest that intensive interventions may be effective in increasing abstinence rates.[54,55] Furthermore, recent data indicate that pairing an intensive smoking cessation program with lung cancer screening may add up to 20% of life expectancy (Figure 5).[51] Specific data on the willingness to participate in a smoking cessation program in the context of lung cancer screening were also generated in a Belgian study. In this study, including about 2700 participants, 84.3% of current or former smokers (N= 1534) answered that they would likely or very likely participate in a screening program for lung cancer. Interestingly, the majority of current smokers that were willing to be screened said they would also want to receive tobacco-use cessation counseling in parallel with screening (71.8%).[56]

"Recent data indicate that pairing an intensive smoking cessation program with lung cancer screening may add up to 20% of life expectancy."

As such, the available data underscore that policy makers should not make a choice for lung cancer screening or investments in smoking cessation, but rather consider lung cancer screening and smoking cessation interventions as complementary interventions.

Figure 5 Expected absolute number of life years gained among current smokers by screening intervention and supplementary or stand-alone smoking cessation support (criteria for lung cancer screening in this trial were: 60–79 years old, at least 35 Packyears or 2.6% PLCOm risk) (reproduced with permission from de Nijs et al.).[51]



3. Optimize participant involvement

At least as important as identifying the right patient population for LDCT lung cancer screening is engaging potential participants to enter the program. In this respect, data from the US indicate that only 10% of the target population is actually entering the screening program. To facilitate a better participation, the invitation for LDCT lung cancer screening should be flanked by well-targeted and easily accessible information campaigns explaining the benefits and potential harms of LDCT lung cancer screening. To maximize the reach of these campaigns, it is important to use different media channels, such as tv, posters in the public space, campaigns on social media, etc. The involvement of communication specialists in setting up these campaigns may prove to be a major asset.

Potential screening participants may also decide not to engage in the program because they are afraid to know the result. In fact, among the general population, a lung cancer diagnosis is still seen as a death sentence. In this respect, it is important to give the message that this is not the case if the lung cancer is diagnosed at an early stage. The involvement of patient organizations in communication campaigns on lung cancer screening may be useful to convince the general population of the curability of lung cancer in an early disease stage.

Reassuringly, results of a cross-sectional study on the acceptability of a lung cancer screening program in Belgium indicate a high willingness to participate. In fact, this study estimated that acceptability of participating in a lung cancer screening program was 92%. In this study, smokers had an acceptability of 97%, as compared to 92% for ex-smokers and 90% for never-smokers.[57]

General practitioners (GPs) can play an important role in mitigating potential fears about screening, provide balanced information about risks and benefits, and explain the importance of early detection in lung cancer. In addition to this, smoking status is mentioned in individual patient files, making it possible for them to search their patient database for active smokers and motivate them to participate in lung cancer screening. GPs may also have an active role in the follow-up of individuals after their first round of screening and explain the findings. Unfortunately, the enthusiasm for LDCT lung cancer screening among GPs is low in Belgium. The main reason for this is related to the

"A major factor standing in the way of participating to lung cancer screening relates to the societal stigma surrounding lung cancer."

added workload that this would bring. Among GPs there is a fear that they will have to play an active role in selecting and contacting active smokers in their patient database. In reality, however, GPs will not have to play a proactive role in the recruitment of patients making this fear unjustified. On the other hand, screening invitations may potentially generate questions, uncertainties, and doubts among patients. The latter would indeed require some additional counseling work for GPs, which comes on top of their already packed workload.[58] To mitigate this, extra support should be offered to GPs to deal with the counselling burden that may come with lung cancer screening.

A second factor that influences the critical appraisal of lung cancer screening by GPs may be a lack of up-to-date education on the proven benefits of LDCT lung cancer screening and on the improvements that have been made in the technology that is used for this screening. In line with this, data from the US show that GPs with a lower knowledge of screening guidelines were less likely to refer patients for LDCT screening.[59] Dedicated education platforms on the benefits and harms of lung cancer screening, involving radiologists and thoracic oncologists, may therefore spur the enthusiasm of GPs. In this, an important emphasis should be put on the difference between low-dose and standard diagnostic CT scans and their respective potential risks (i.e., radiation exposure). Furthermore, GP education should also discuss the therapeutic advances that have been made in the management of lung cancer, with a clear emphasis on the difference in intensity and curative potential of the treatments that are currently used for lung cancer in an early and advanced stage.

Importantly, we must emphasize that the first line of care is not limited to GPs alone. Given the skepticism of GPs concerning lung cancer screening, it will be important to also involve other elements in the first line care in the implementation of a lung cancer screening program, such as pharmacists, OCMW/CPAS (Openbaar Centrum voor Maatschappelijk Welzijn/ Centre Public d'Action Sociale) or the CAW (Centrum Algemeen Welzijnswerk).

A major factor standing in the way of participating to lung cancer screening relates to the societal stigma surrounding lung cancer. In fact, the general public tends to hold smokers responsible for their disease, while many patients have feelings of guilt or shame. To dispel these misconceptions, there is a need for educational campaigns underscoring the fact that smoking is more than just a lifestyle choice, but a serious addiction. Of note, the stigma surrounding smoking is not only a problem in the general population, but also at a policy level. In fact, the willingness to invest in lung cancer screening may be impacted by this stigma: "why should we invest in a screening program for people who willingly increased their risk?" Interestingly, results from a Belgian survey among 2700 individuals indicate that 83.6% of all respondents (smokers, ex-smokers and never smokers) believed that offering lung cancer screening to current or former smokers is a good idea.[56]

A potential strategy to reduce the stigma of "smoking behavior" with respect to lung cancer causality could be to make a strong statement on the responsibility of the tobacco industry and its commercial activities as the driver of the tobacco epidemic.[60] The importance of 'stigma reduction' was also illustrated by a large survey in England which showed that minimizing stigma related to cancer risk in smokers was essential to improve participation.[61] It is clear that completely removing the smoking stigma requires a profound mentality shift in the population. However, small measures can already help a lot. For example, in the UK they have incorporated lung cancer screening in a more general "lung health check". This approach promotes a more positive view of the screening which may encourage more people to participate.

Equity is a key parameter by which the success of a population-based screening program should be measured. Nevertheless, international data show that there tends to be an over-representation of participants with a high social economic status among participants in screening programs.[62] To overcome this, screening programs should include targeted efforts to engage hard-to-reach population groups, such as people with a lower socio-economic status. Reaching these populations is of particular relevance in the context of lung cancer, given the higher prevalence of risk factors (mainly smoking) in marginalized populations. Furthermore, data from pilot and real-world studies show that people with a lower socio-economic status or other disadvantages are less likely to participate in cancer screening programs.[63,64] The latter is also reflected by the results of the Belgian acceptability study which indicated that a lower income and a lower level of education were among the more important factors negatively influencing acceptability.[57] As classical campaigns often fail to reach these populations and given the fact that people with a lower socio-economic status don't tend to visit their GP on a regular basis (if at all), there is a need for innovative ways of communication and new outreach strategies.

"Several research groups are evaluating whether artifical intelligence can be introduced into the evaluation of CT scans, which would markedly reduce the workload that lung cancer screening would impose on radiologists."

4. Provide substantial screening capacity & expertise

Implementing a screening program requires many resources, not only in terms of money but also in terms of workforce and technical capacity. A screening program involves a series of activities, such as identification of the potentially eligible population, providing accurate information about the benefits and harms, organization of the screenings, performing the LDCT scan, interpreting results, conducting follow-up tests, providing counselling and treatment, and managing patient data. All these activities require a skilled workforce, including radiologists, radiology technicians, pulmonologists, thoracic surgeons, oncologists, nurses, and administrative staff. When considering the implementation of a lung cancer screening program, it is important to assess the capacity of the workforce involved in all stages of the process, and to ensure that services have the capacity to deal with additional referrals.

While Belgium has a large capacity of CT scans, a nationwide targeted screening program would inevitably put substantial pressure on this capacity. It is self-evident, that we must avoid that the screening of healthy individuals fills up slots for patients who urgently need a CT scan. A conservative estimate suggests that screening an at-risk population of (ex)-smokers would require 140,000 to 250,000 CT scans per year when a 50% participation rate is assumed. For the moment, we are only at about 60% of this capacity in Belgium, illustrating the need to increase the CT capacity ahead of implementing a lung cancer screening program. In addition to this, lung cancer screening will also lead to a higher need for surgical capacity including an increased number of hospitalizations.

Expertise in reading lung cancer CT scans plays an important role in distinguishing non-nodular opacities, scars, atelectasis, intrapulmonary lymph nodes or fat-containing hamartomas from typically malignant nodules. To date, however, there are few radiologists that are adequately trained for lung cancer screening. Therefore, education, training, certification and quality assurance of reading radiologists is warranted. The latter is of particular importance to avoid 'over-calling', which might result in over-investigation of minor findings or overtreatment of findings that can be controlled by active surveillance.[65] To assist in this, the European Society of Thoracic Imaging has recently developed a lung cancer screening certification program based on e-learning and workshops, and validated by a final examination. In addition to this, several research groups are evaluating whether artificial intelligence can be introduced into the evaluation of CT scans, which would markedly reduce the workload that lung cancer screening would impose on radiologists.[66]

5. Develop effective care pathways

The success of a screening program is highly dependent on the existence of high-quality care pathways. The result of the screening must be communicated to the participant as soon as possible, with a clear description of the potential consequences of the result. Of note, the GP can play an important role in explaining this in more detail to the participant should he/she have additional questions. Anyone with a positive result should have rapid and equitable access to a comprehensive diagnosis of the disease and a structured care pathway led by a multidisciplinary care team.[63]

In parallel with effective care pathways for lung cancer, the program should also include a clear protocol on how to deal with incidental findings (i.e., findings on thoracic CT unrelated to the primary purpose of identifying lung cancer). Given the nature of the investigations that are used for lung cancer screening (i.e., LDCT), incidental findings are more common than in screening programs for colon or breast cancer. The prevalence of incidental findings in the thorax, as well as in adjacent neck or abdominal regions, differs significantly across the different screening trials, with rates ranging from 8% to 94%.[67,68,69] The most common of these incidental findings can be found in the cardiovascular system, but also renal, hepatic or pulmonary lesions can be detected. In the context of a cost-effectiveness analysis of LDCT lung cancer screening in Belgium, the KCE estimated that approximately a quarter of screening participants (23%) would require an additional examination for incidental findings.[70]

The management of incidental findings detected during lung cancer screening is a determining factor for the overall effectiveness of the program and its cost-effectiveness. In an attempt to standardize the reporting and management of incidental findings a task force from the European Respiratory Society (ERS) proposed a standardized approach of reporting and managing incidental findings.[71] In this effort, they identified 23 categories of incidental findings and provided suggestions for reporting and follow-up actions when these incidental findings are encountered.[71]

According to the stakeholders that were consulted for this report, you have to make a distinction between potentially malignant findings, and other entities like coronary calcification and emphysema. Not reporting the former may be challenging from an ethical point of view. However, we must underscore that the screening is done using LDCT without any contrast. As a result, there is a high likelihood that these incidental findings are in fact noise and turn out to be benign. As such, it seems wise to be restrictive to report these additional items. With respect to coronary calcification and emphysema there is no scientific evidence showing a benefit of reporting this and for this reason, the Flemish implementation study for lung cancer screening will not mention these findings on the report. With lung cancer screening the aim is to improve the health of the population, not of the individual. This fact always has to be kept in mind when discussing incidental findings.

6. Ensure quality & performance management

For a screening program to be effective, it should be linked to a dedicated system of program planning, monitoring and evaluation to ensure ongoing quality control and achievement of performance targets.[26] To facilitate this, there is a need for a performant IT system and continuous data collection. Monitoring and evaluation of screening programs is necessary to ensure that the screening programs are as effective as expected and to ensure public trust in the program. Importantly, the regional agencies in Belgium that are currently responsible for the organization of other national cancer screening programs (colorectal, breast) have experience in such a performance management and should be consulted when plans for a national lung cancer screening are unfolded.

The economic reality of lung cancer screening

Setting up a national program for lung cancer screening will require a significant investment, with the financial rewards of this investment only becoming apparent after a certain period of time.

As such, the decision to engage in a national LDCT lung cancer screening will have a profound impact on an already stretched, healthcare budget. In Belgium, this situation is further complicated by an inappropriate distribution of competences between the federal and regional governments in a sense that preventive care falls under the responsibility of the regional entities, whereas some of the related procedures remain under the responsibility of the Federal State.

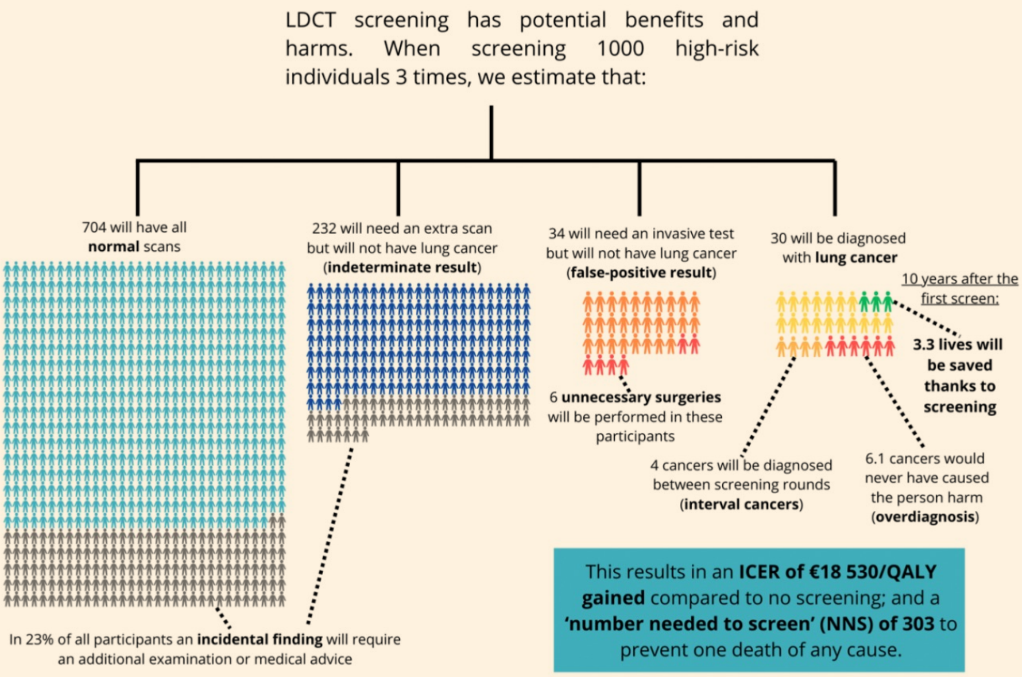
More specifically, the regions are in charge of organizing cancer screening programs, while the federal INAMI/RIZIV deals with the reimbursement of the examinations that are used for this screening (i.e., LDCT in the context of lung cancer screening). As a result, the governmental entity that would be responsible for organizing the screening program in Belgium (i.e., the regions), will in the end not reap the benefits of the lower treatment costs associated with an earlier detection of lung cancer (healthcare expenditures are a federal competence). This complex governmental structure in Belgium makes it challenging to organize cancer screening in a structured and effective way.

Given the link between smoking and lung cancer, some have argued that the costs for lung cancer screening should be borne by the tobacco industry. However, in doing so, you create the impression that the tobacco industry can be part of the solution, while they are clearly the main driver of the problem. A more sensible approach to have the tobacco industry pay their debt could be to further increase the excise on tobacco products and put this extra revenue to partially fund the screening program.

From an economic point of view, an efficient use of limited resources should prioritize the cost-effectiveness of an intervention (i.e., the expected incremental costs of the intervention in relation to the expected incremental benefits) over its budget impact. Over the years, several attempts have been made to evaluate the cost-effectiveness of LDCT lung cancer screening. In this respect, an analysis of the NLST data resulted in a cost of 81,000 USD per gained quality adjusted life year (QALY), which proved to be well below the reasonable threshold of cost-efficiency in the USA (100,000 USD per QALY gained).[72] In addition to this, several European cost-effectivity analyses have indicated that LDCT lung cancer screening can be cost-effective in different healthcare systems, depending on factors such as inclusion criteria, established algorithms for positive screen results, screening intervals and tobacco cessation interventions.[73,74,75]

Very recently, the KCE published their cost-effectiveness analysis of LDCT lung cancer screening for the Belgian context.[70] For this analysis, the investigators used data from the NELSON trial, assuming a participation rate of 51% and an overdiagnosis rate of 23%. To compensate for price reductions of systemic therapies as a result of managed entry agreements between the federal government and pharmaceutical companies, the cost for systemic therapy was reduced by 40%. This analysis indicated that lung cancer screening would result in an incremental cost of 77,747 Eur per 100 participants and 4.64 QALYs gained per 100 participants. In turn, this translates into an incremental cost-effectiveness ratio (ICER) of 18,530 Eur/QALY gained compared to having no lung cancer screening and a NNS of 303 to prevent one death of any cause. Considering a willingness to pay threshold of 10,000, 20,000 or 30,000 Eur per QALY gained this

Figure 6 1000-person figure on the benefits and harms of LDCT as calculated by the KCE, considering an overdiagnosis rate of 23% (data provided by the Belgian Health Care Knowledge Centre [KCE]. Reproduced with permission).[70]



would lead to 1.5%, 72% or 94% probability of being cost-effective, respectively.[70] The expected benefits and harms of LDCT lung cancer screening under this scenario are clearly illustrated by the 1000-person graph depicted in **Figure 6**.

Of note, the factors having the biggest impact on the ICER in this analysis were the rate of overdiagnosis and the discount rate that is negotiated for the systemic therapies. In fact, the greater the discounts obtained by the government, the less cost-effective the lung cancer screening program proves to be. In addition to this, also the participation rate had a remarkable effect on the cost-effectiveness of the screening program, with a higher cost-effectiveness in case of a higher participation rate. Of note, the impact of incidental findings was not included in this model due to a lack of evidence on its impact. Further research will be required to quantify the health gains or losses of incidental findings associated with LDCT screening.[70]

Conclusions

1. **LDCT lung cancer screening can save lives.** As such, setting up a lung cancer screening program is a fight worth fighting.

2. Not investing in a structured lung cancer screening program will form the basis for *ad hoc* screening initiatives that lack **standardization and quality control.**

3. **Lung cancer screening should ideally be organized through a network of expertise centers**, assuring adequate quality control along the entire screening process and subsequent investigations.

4. **The first line of care will have to play an important role in setting up a lung cancer screening program.** As such, GPs, pharmacists, and all other components of this first line of care need to be closely involved.

5. To increase the enthusiasm for lung cancer screening among the first line of care there is a **need for balanced educational material** clearly discussing the potential benefits and harms of lung cancer screening.

6 **There is a need for more education on lung cancer among the general population.** By emphasizing the multifactorial nature of lung cancer, the smoking stigma can be reduced. Furthermore, by underscoring the curative options for early-stage lung cancer, you can eradicate the misconception that lung cancer is an immediate death sentence.

7 **A lung cancer screening program should always be flanked by a structured smoking cessation program.** In doing so, the screening will become a teachable moment on the possibilities of smoking cessation.

8 **The success of a screening program is highly dependent on the existence of high-quality care pathways.**

9 **A cost-effectiveness study indicates that lung cancer screening can be cost-effective if the policymaker's willingness to pay ranges between €20 000 and €30 000 per QALY gained.** The government now needs to decide if they are willing to make this investment.

10 **Implementation studies for lung cancer screening are warranted and will generate a wealth of data on the efficacy, feasibility, and participation rate.**

Addendum

List of consulted stakeholders

- **ALK Positive Belgium**
- **Belgian Cancer Registry** (BCR)
- **Dr. Aboubakar Nana Frank** (Cliniques Universitaires St.-Luc, Brussels)
- **Prof. Dr. Thierry Berghmans** (Jules Bordet Institute, Brussels)
- **Dr. Christophe Compère** (CHIREC Hospitals Group, Brussels)
- **Dr. Kristof Cuppens** (St. Trudo Ziekenhuis, Sint-Truiden & Jessa Hospital, Hasselt)
- **Prof. Dr. Ingel Demedts** (AZ Delta Roeselare)
- **Dr. Jean-Baptiste Duquenne** (Clinique CHC MontLégia, Liège)
- **Foundation against Cancer**
- **Prolong VZW**
- **Prof. Dr. Annemiek Snoeckx** (Antwerp University Hospital and University of Antwerp, Antwerp)
- **André Stoop** (Lung cancer survivor)
- **Prof. Dr. Guido Van Hal** (Task Force Lung Cancer Screening/Universiteit Antwerpen, Antwerp)
- **Prof. Dr. Jan Van Meerbeeck** (Antwerp University Hospital and University of Antwerp, Antwerp)
- **Prof. Dr. Paul Van Schil** (Antwerp University Hospital and University of Antwerp, Antwerp)

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