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ABSTRACT Lung cancer is the most frequently fatal cancer, with poor survival once the disease is advanced. Annual low dose computed tomography has shown a survival benefit in screening individuals at high risk for lung cancer. Based on the available evidence, the European Society of Radiology and the European Respiratory Society recommend lung cancer screening in comprehensive, quality-assured, longitudinal programmes within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres. Minimum requirements include: standardised operating procedures for low dose image acquisition, computer-assisted nodule evaluation, and positive screening results and their management; inclusion/exclusion criteria; expectation management; and smoking cessation programmes. Further refinements are recommended to increase quality, outcome and cost-effectiveness of lung cancer screening: inclusion of risk models, reduction of effective radiation dose, computer-assisted volumetric measurements and assessment of comorbidities (chronic obstructive pulmonary disease and vascular calcification). All these requirements should be adjusted to the regional infrastructure and healthcare system, in order to exactly define eligibility using a risk model, nodule management and quality assurance plan. The establishment of a central registry, including biobank and image bank, and preferably on a European level, is strongly encouraged.

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## Introduction

Lung cancer causes 1.37 million deaths per year worldwide, which represents 18% of all cancer deaths [1]. Within the European Union, lung cancer is the most frequently fatal cancer, leading to over 266 000 deaths yearly and accounting for 20.8% of all cancer deaths [2]. Definitive surgery in the early stages is the most effective treatment for lung cancer. However, most patients are diagnosed at an advanced, and thus non-curable, disease stage. Survival time decreases significantly with progression of disease, with a 5-year survival time declining from 50% for clinical stage IA to 43%, 36%, 25%, 19%, 7% and 2% for stages IB, IIA, IIB, IIIA, IIIB and IV, respectively [3]. Moreover, Shi *et al.* [4] reported a 5-year survival rate of more than 80% in 185 surgically treated patients with peripheral small-sized lung cancers (2 cm or less) after lobectomy and lymph node dissection. In particular, the 5-year survival rate increased with smaller tumour size: 80% in tumours 1.6–2.0 cm, 85% in tumours 1.0–1.5 cm and 100% in tumours <1.0 cm in diameter, respectively. It is therefore crucial to detect lung cancer early, before symptoms occur and while curable therapy is still achievable.

During the past decade, several studies focused on the yield of low dose computed tomography (LDCT)-based screening for lung cancer. In total, roughly 100 000 high risk individuals were screened for lung cancer by LDCT. The largest randomised trial, the US-based National Lung Screening Trial (NLST), has shown a survival benefit for annual LDCT, with a 20% reduction of the lung cancer related mortality, whereas the all-cause mortality decreased by 6%. However, there is still some debate associated with the appropriate algorithm to select the screening cohort, as well as with how exactly the images should be read. The second largest study, the European NEderlands-Leuvens Screening ONderzoek (NELSON) trial, will be finalised by the end of 2015 and will add insight, probably with a more accurate screening algorithm and lower rate of false positivity, as discussed by Shlomi *et al.* [5].

As the results of this large European study are pending and the screening algorithms used in published studies have not been universal, there are numerous issues that should be taken into consideration before starting a LDCT screening programme in Europe. This paper will review the current status of lung cancer screening and provide recommendations for the standards and additional evidence required.

## Status quo

### *Results of the current trials*

The NLST is the first randomised controlled lung cancer screening trial in current and former smokers (>30 pack-years) aged between 55 and 74 years, to show a significant reduction in lung cancer-specific mortality [6]. The computed tomography (CT) screening arm of the trial involved 26 722 participants who received three yearly screening rounds of LDCT. The control arm involved 26 732 participants who received three yearly screening rounds using chest radiographs. After a follow-up period of approximately 6.5 years, participants in the CT screening arm were 20% less likely to die from lung cancer than those in the control arm. A 6% reduction in overall mortality was also observed within the 6.5-year period. In the CT screening arm, 356 participants died from lung cancer, whereas the number in the corresponding radiography arm was 443 [6]. In an additional evaluation 1 year later, these numbers had increased to 469 in the CT arm and 552 in the radiography arm, which corresponds to a 15% reduction [7]. These results suggest that LDCT finds more cancers, most of them being in stage IA (>50%) and approximately 10% in stage IB [8]. Still, 43% (469 out of 1089) of those patients who developed lung cancer died of lung cancer. The overall screening effort meant that 320 participants had to be screened to prevent one lung cancer death within the 6.5-year follow-up period [6].

The Dutch–Belgian NELSON trial is the largest European randomised controlled trial with at-risk participants based on age and smoking history randomly selected from population registries. The first outcome data are expected in 2016. The trial involves 7577 participants in the CT screening arm and compares them to 7871 participants in the control arm [9]. Apart from a smoking cessation programme, no intervention was offered in the control arm. Published results are available from smaller randomised

KEY POINTS

- Lung cancer screening using low dose computed tomography reduces mortality
- Leading US medical societies recommend large scale screening for high risk individuals
- There are no lung cancer screening recommendations or reimbursed screening programmes in Europe as yet
- The European Society of Radiology and the European Respiratory Society recommend lung cancer screening within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres
- High risk, eligible individuals should be enrolled in comprehensive, quality-controlled longitudinal programmes

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controlled trials from Denmark (DLST) and Italy (Italung, DANTE and MILD). These trials involved approximately 1000–2000 patients in each arm [10]. Published results suggest no advantage for lung cancer screening. In fact, DLST and MILD even found a trend towards higher mortality in the yearly CT screening arms [11, 12]. Other current randomised controlled trials are the German Lung Screening and Intervention (LUSI) trial and the UK Lung Screening (UKLS) trial [13, 14].

### *Current recommendations*

There is a wide range of acceptance of the general lung cancer screening algorithm using LDCT across the globe; however, different degrees of modification from the NLST algorithm seem to be required (table 1) [5].

From February 2012, the Lung Cancer Screening Panel of the National Comprehensive Cancer Network (NCCN) in the USA recommended annual LDCT screening of all high risk individuals between the age of 55 and 74 years, as defined in the NLST [15]. However, the NCCN guidelines expanded the NLST criteria based on non-randomised studies and observational data. Individuals 50 years of age or older with a tobacco smoking history of 20 or more pack-years and one additional risk factor should be annually screened. The suggested additional risk factors were history of cancer, history of lung disease (chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis), family history of lung cancer, radon exposure and occupational exposure. The NCCN currently does not advise screening of individuals at moderate and low risk for lung cancer or for individuals with exposure to second-hand smoke [16].

A collaborative initiative of the American Cancer Society [17], the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology [18], and the NCCN published a review of LDCT screening for lung cancer together with clinical practice guidelines in May 2012 [10]. They adopt the NLST eligibility criteria, but note that the duration and frequency of screening remain undetermined [18]. In June 2012, guidelines for lung cancer screening were issued by the American Association for Thoracic Surgery (AATS) [19], expanding the criteria beyond the NLST. The AATS guidelines consider the amount of tobacco exposure and age to be the most important risk factors and therefore do not restrict screening to patients who quit smoking in the previous 15 years. Since the risk of lung cancer does not decrease after 3 years of screening, the AATS recommends annual LDCT screening for high risk patients from age 55 to

TABLE 1 Eligibility criteria for early detection of lung cancer by low dose computed tomography, according to guidelines issued in 2012–2013 by various organisations [5]

| Guidelines by organisation | Date | Age years | Smoking history pack-years | Smoking cessation years | Category/ level |
|---|---|---|---|---|---|
| **NCCN** | Jan 2015 | 55–74 | ⩾30 | <15 | 1 |
| | | ⩾50 | ⩾20 (and one additional risk factor[#]) | | 2A |
| **ALA** | Apr 2012 | 55–74 | ⩾30 | <15 | NA |
| **Collaborative work of ACCP/ASCO/NCCN** | May 2012 | 55–74 | ⩾30 | <15 | 2B |
| **AATS** | June 2012 | 55–79 | ⩾30 | Any active or former smoker | 1 |
| | | 50–79 | ⩾20 and added risk ⩾5% of developing lung cancer within 5 years[¶] | | 2 |
| | | Any | Any and ⩾4 years remission after bronchogenic carcinoma | | 3 |
| **ACS** | Jan 2013 | 55–74 | ⩾30 | <15 | NA |
| **ACCP** | May 2013 | 55–74 | ⩾30 | <15 | 2B |
| **USPSTF** | July 2013 | 55–79 | ⩾30 | <15 | B |

NCCN: National Comprehensive Cancer Network; ALA: American Lung Association; ACCP: American College of Chest Physicians; ASCO: American Society of Clinical Oncology; AATS: American Association for Thoracic Surgery; ACS: American Cancer Society; USPSTF: US Preventive Services Task Force; NA: not available. Levels of evidence: category 1: based upon high level evidence, there is uniform consensus that the intervention is appropriate; category 2A: based upon lower level evidence, there is uniform consensus that the intervention is appropriate; category 2B: based upon lower level evidence, there is consensus that the intervention is appropriate; category 3: based upon any level of evidence, there is major disagreement that the intervention is appropriate. [#]: radon exposure, occupational exposure (silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel fumes and nickel), cancer history (survivors of lung cancer, lymphomas, cancers of the head and neck, or smoking-related cancers), family history of lung cancer, disease history (chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis; [¶]: such as COPD with forced expiratory volume in 1 s of 70% or less than predicted, environmental or occupational exposures, any prior cancer or thoracic radiation, genetic or family history.


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79 years. They consider that level 2 evidence is enough to advise screening for smokers 50–79 years of age with a 20 pack-year smoking history or other factors that produce a cumulative ⩾5% risk of developing lung cancer over the following 5 years. Based on AATS consensus opinion (level 3 evidence), patients treated for primary bronchogenic carcinoma who have completed 4 years of radiographic surveillance without evidence for recurrence should also be screened. In January 2013, the American Cancer Society published guidelines that recommend annual lung screening by LDCT based on the NLST eligibility criteria until the age of 74 years [20]. In May 2013, the ACCP published its third edition guidelines of diagnosis and management of lung cancer, including a recommendation concerning lung cancer screening [21, 22]. Annual screening with LDCT for individuals who meet the NLST eligibility criteria is recommended (grade 2B; weak recommendation, moderate level of evidence).

In December 2013, the United States Preventive Services Task Force (USPSTF) developed their recommendation statement [23], which was published in March 2014 [24], supporting LDCT lung cancer screening for healthy adults between 55 and 80 years of age with a smoking history of 30 pack-years or more and who have smoked within the previous 15 years. The number of years needed for screening is not specified, but screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits the life expectancy or the ability or willingness to have curative lung surgery (grade B recommendation). Under the Affordable Care Act [25], any procedure that receives a grade B recommendation from the USPSTF has to be covered by private insurers without co-payment. Most insurers in the USA follow the recommendations of the task force, and pay for those services. In April 2014, the US federal agency Center for Medicare and Medicaid services (CMS) advisory panel voted against covering lung cancer screening [26]. Key concerns were the high false-positive rate of CT screening, indication creep outside of the intended screening population, inability to assure quality scans with low radiation dose, and consistent interpretation and diagnostic work-up in routine practice. In February 2015, in contrast to the recommendations of the agency's advisory board, Medicare announced its decision to start covering annual lung cancer screening once per year for long-time smokers at high risk for the disease [27]. CMS experts require that screening candidates are between ages 55 and 77 years, have no signs or symptoms of lung disease, have tobacco smoking history of at least 30 pack-years and are current smokers or ex-smokers who have quit smoking within the previous 15 years. For the initial screen, the beneficiary must receive a written order for LDCT lung cancer screening obtained during a "lung cancer screening counselling and shared decision-making visit" from a physician, physician assistant, nurse practitioner or clinical nurse specialist. CMS also gives details for that visit, radiologist eligibility criteria and imaging centre eligibility criteria [27]. In Europe, there are no lung cancer screening recommendations or reimbursed screening programmes so far.

## Challenges

### *Pre-test probability*

Tobacco smoking is a major risk factor for lung cancer as shown by many epidemiological studies. Other less important risk factors are passive (second-hand) smoking, occupational exposure, environmental exposure, residential radon exposure, presence of COPD and family history of lung, head and neck cancer. A meta-analysis of 10 case–control studies including 7609 cases and 10 431 controls shows an increase of the relative risk of lung cancer in the European population with active smoking (*versus* ex-smokers), with duration and amount of smoking and the cumulative dose of pack-years [28]. The recommendations for the NELSON trial are based on data from the Cancer Prevention Study II (CPS II) [29]. According to this data, a smoking history of 30 years or more in individuals older than 55 years and a consumption of at least one pack of cigarettes a day correspond to a lung cancer incidence of at least 300 per 100 000. The rate of lung cancer diagnosed in recent randomised trials by LDCT for those selected populations are summarised in table 2.

More data from other cohorts are described in the systematic review published by Bach *et al.* [10]. The rate of lung cancer diagnosed ranges between 0.8 and 2.2% initially and between 2.4% and 4.7% in 34–78 months of follow-up. Those figures can be taken as the pre-test probability.

### *Overdiagnosis*

The detection of small lesions confirmed to be malignant but which do not grow, spread, or cause death is referred to as overdiagnosis. This includes patients who are destined to die from another cause, *e.g.* comorbidity or an unexpected event, in addition to slow growing/non-spreading cancers [10]. Overdiagnosis represents an important potential harm of screening, since it incurs additional cost, anxiety and morbidity associated with the cancer treatment. During earlier screening trials using chest radiographs in the Mayo and the Czechoslovakian randomised trials, substantially more cancers (20%) were detected in the screened, than in the unscreened group [30, 31]. Nearly all of the excess cancers detected in the screened group in the Mayo clinical trial were early stage cancers. However, the failure to detect early stage

TABLE 2 Selection criteria, number of enrolled individuals and the rate of diagnosed lung cancer of major randomised controlled trials

| Study | Selection criteria | | Patients screened n (follow-up) | Lung cancer diagnosed at initial screening (total in follow-up) |
|---|---|---|---|---|
| | Age years | Tobacco smoking (delay since weaning) | | |
| **DLCST** | 50–70 | ⩾20 pack-years (0–9 years) | 2052 (58 months) | 0.8% (3.4%) |
| **DANTE** | 60–74 (only men) | ⩾20 pack-years (0–9 years) | 1276 (34 months) | 2.2% (4.7%) |
| **ITALUNG** | 55–69 | ⩾20 pack-years (active or former) | 1406 (36 months) | 1.5% (2.8%) |
| **MILD** | ⩾49 | ⩾20 pack-years (0–9 years) | 1190[#] (120 months)<br>1186[¶] (53 months) | 0.8% (2.4%) |
| **NELSON** | 50–75 | ⩾15 pack-years[+] (0–9 years) | 7907 (60 months) | 0.9% (2.6%) |
| **NLST** | 55–74 | ⩾30 pack-years (0–15 years) | 26 722 (78 months) | 1.1% (2.4%) |

[#]: annual computed tomography; [¶]: biannual computed tomography; [+]: NELSON inclusion criteria: number of cigarettes smoked is ⩾ 15 per day for 25 years OR ⩾10 cigarettes per day for 30 years AND still smoking or have quit <10 years ago.

cancers in the control group was without apparent ill effect: the control group experienced no excess number of lung cancer deaths [30]. The results were generally confirmed by the Czechoslovakian study. Both studies suggest that screening is detecting "excess" lesions, which probably would not progress to advanced/lethal disease [30, 31]. The PLCO trial [17] examined 155 000 subjects in the general population and found 18 excess lung cancers in the chest radiography group (compared with no chest radiography group) after 6 years of follow-up (2 years after screening ended) and 76 lung cancers after 13 years of follow-up. Data from the same trial, evaluating overdiagnosis among a high risk population only, showed a cumulative incidence of lung cancer of 606 per 100 000 person-years in the chest radiography group and 608 per 100 000 person-years in the usual care group after 6 years of follow-up.

The overdiagnosis rate for LDCT screening cannot yet be estimated [24]. The NLST data shows a persistent gap of about 120 excess lung cancers in the LDCT *versus* the chest radiography arm, but further follow-up is needed [32]. In both groups, the percentage of stage IA and stage IB lung cancers was high. Relative to the issue of overdiagnosis, fewer stage IV cancers were detected in the LDCT group than in the chest radiography group at the second and third screening rounds in the DANTE trial, where 2472 subjects were screened with chest radiography and sputum cytology at baseline and randomised afterwards to yearly LDCT or clinical follow-up. Lung cancer prevalence in the control chest radiography arm was 0.67% (n=8) and 50% of these patients had stage I cancer, while the prevalence in the CT group was 2.19% (n=28) with 57% stage I cancer, respectively. It has to be noted that 13 of the 28 LDCT lung cancer cases had already abnormal chest radiography findings at baseline [33].

Still, most lung cancer prevention experts think lung cancer screening leads to overdiagnosis, but many clinicians believe it does not [34]. Death rates from lung cancer imply that essentially all histological foci of lung cancer pose a threat to health, irrespective of their CT phenotype or how they are discovered. In the NLST, the size of the nodule and whether it is solid or sub-solid mattered. However, whether this appearance is linked to higher overdiagnosis probability remains to be concluded. Based on the Pan-Canadian early Detection of Lung Cancer Study (PanCan), McWilliams *et al.* [35] presented a model to predict a cancerous pulmonary nodule (*versus* benign). Predictors for cancer were older age, female sex, family history of lung cancer, emphysema and larger nodule size, location of the nodule in the upper lobe, part-solid nodule type, lower nodule count and spiculation. Adopting such a model may direct the clinicians in their follow-up management.

### *Risk models*

Risk models help to increase pre-test probability and reduce overdiagnosis. They improve the patient selection in order to define populations with higher pre-test probabilities: the Liverpool Lung Project (LLP) risk prediction model is used in the UKLS screening trial; the PLCO2012 (Prostate, Lung, Colorectal, and Ovarian) randomised trial and the NLST trial. The former two studies predict lung cancer detection while the latter predicts death by lung cancer (table 3).

Recently, de Koning *et al.* [39] published a study estimating the harms and benefits of lung cancer screening for efficient lung cancer screening policies. They used five separately developed micro-simulation models calibrated to the two largest randomised, controlled trials on lung cancer screening [17, 39]. Those models

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TABLE 3 Risk prediction models used in different lung cancer screening trials

| Model | Risk factors included | Period of prediction of lung cancer diagnosis or death | Reference for algorithm |
|---|---|---|---|
| **LLP (detection)** | Age<br>Sex<br>Years of smoking<br>Family history of lung cancer by age of affected relatives<br>History of a previous cancer<br>History of pneumonia<br>History of exposure to asbestos | 5 years | Raji *et al.* [36] |
| **PLCO (detection)** | Age<br>Race/ethnicity<br>Education<br>Body mass index<br>Chronic obstructive pulmonary disease<br>Personal history of cancer<br>Family history of lung cancer<br>Smoking status (current *versus* former)<br>Smoking intensity (average cigarettes/day)<br>Smoking duration<br>Smoking quit time | 6 years | Tammemägi *et al.* [37] |
| **NLST (death)** | Age<br>Sex<br>Ethnicity<br>Body-mass index<br>Pack-years of smoking<br>Years since smoking cessation<br>Presence of emphysema<br>First-degree relative with lung cancer | 5 years | Kovalchik *et al.* [38] |

were independently developed in five institutions: Erasmus Medical Center (Rotterdam), Fred Hutchinson Cancer Research Center (Seattle), Massachusetts General Hospital (Boston), Stanford University (Stanford), and University of Michigan (Ann Arbor). All account for the individual's age-specific smoking-related risk for lung cancer, date and stage of lung cancer diagnosis, the corresponding lung cancer mortality and the individual's life expectancy in the presence and absence of screening. The most advantageous strategy identified is the annual screening from ages 55 through 80 years for ever-smokers with a smoking history of at least 30 pack-years and ex-smokers with less than 15 years since quitting. That approach would lead to 50% of cases of cancer being detected at an early stage (stage I/II), 575 screening examinations per lung cancer death averted, a 14% reduction in lung cancer mortality, 497 lung cancer deaths averted, and 5250 life-years gained per the 100 000-member cohort. Harms would include 67 550 false-positive test results, 910 biopsies or surgeries for benign lesions, and 190 overdiagnosed cases of cancer (3.7% of all cases of lung cancer).

So far there are no good risk predictors for nonsmokers and no convincing data to recommend screening. Lung cancer in never smokers is the seventh leading cause of cancer mortality and therefore is a significant cause of death worldwide. The main risk factors include age, environmental tobacco exposure, cooking fumes, inherited genetic susceptibility, occupational and environmental exposure to carcinogens, hormonal factors, pre-existing lung disease and oncogenic viruses [40]. Nonsmall cell lung cancer (NSCLC) in never smokers is clinically characterised by an increased incidence in females and a higher occurrence of adenocarcinoma in comparison to NSCLC in ever smokers in both surgical patients and non-resectable advanced stage patients [41]. Even though those factors are known, there is no beneficial screening programme for lung cancer among this population.

### *False positives and complications during work-up*

With modern multidetector CT, pulmonary nodules are detectable at a size of less than 2 mm. Small nodules are extremely common but the vast majority of these nodules are benign. Given this fact, the definition of a positive screening result determines the number of false-positive results. On average, about 25% of the thoracic surgical procedures performed during the various randomised controlled lung cancer screening trials were done for benign nodules [21]. If there are fewer false-positive nodules, there is less need for further work-up and the risk of complications, especially from invasive diagnostic examinations including surgery.

The definition of a positive screening result differed substantially between the NLST and most European trials. The NLST defined any non-calcified nodule with a maximum diameter ⩾4 mm as a positive screening result [6]. As a consequence, the number of false-positive scans was high: 27% of scans in the first two screening rounds, of which 96% were false-positive. According to the NLST nodule management algorithm, these suspicious nodules needed further work-up, either a follow-up LDCT for nodules of 4–10 mm or a referral to a pulmonologist for nodules >10 mm in maximum diameter [6].

The NELSON and some other European trials used a threshold of approximately 10 mm diameter (50 $mm^3$ volume) for a positive screening result but also established an indeterminate group of nodules measuring 5–10 mm in diameter (50–500 $mm^3$ volume) that required earlier follow-up than the yearly screening interval [42]. Only if significant growth (>25% volume change) was found, these nodules were considered a positive screening result. By using this approach, the number of scans with positive screening results was reduced from 27% in the NLST to 2.7% in the NELSON, and the false-positives could be reduced substantially from >95% in the NLST to approximately 50% in the NELSON [8, 43].

Recently, new criteria for the follow-up of pulmonary nodules, such as LungRADS and LU-RADS, have been presented in order to increase the positive predictive value in CT screening with minimum effect on sensitivity for the detection of malignancy [44, 45].

The size of a nodule was measured in most screening trials, like the NLST, as the largest diameter of a pulmonary nodule [6]. This approach suffers from a substantial inter- and intra-reader variability, which can be reduced by applying volumetric techniques as are used in the NELSON and other more recent trials. Non-actionable nodules were defined as such with benign morphology (*e.g.* calcification), small size (<50 $mm^3$), and lack of or very slow growth of the solid component of a nodule with a volume doubling time (VDT) >600 days. Indeterminate nodules were defined as nodules with a volume of the solid component between 50 and 500 $mm^3$, sub-solid nodules with a diameter of the ground glass component >10 mm, or solid nodules with a VDT between 400 and 600 days. Actionable nodules were defined as solid components >500 $mm^3$, more than 20% growth in diameter of a ground glass component or VDT <400 days of a solid component [42]. Non-actionable, reportable nodules were kept on regular (yearly) follow-up, indeterminate nodules were put on a more rapid follow-up of 3–6 months, while actionable nodules led to direct medical work-up.

Increasing knowledge about the CT phenotypes of screen-detected pulmonary nodules with different biologic behaviour will lead to a better estimation of their probability of malignancy and help to decrease the amount of additional follow-up scans and work-up examinations [46], *e.g.* perifissural nodules were demonstrated to have a high likelihood of being benign [47, 48].

For the invasive diagnostic work-up of small nodules, the value of white light fibrebronchoscopy is very limited [49], but newer diagnostic endoscopic techniques, such as endobronchial ultrasound-guided biopsy with mini probe or electromagnetic navigation bronchoscopy, might be more promising. For some peripheral nodules (>1 cm), transthoracic CT-guided biopsy or primary resection by video-assisted thoracoscopic surgery for diagnostic and therapeutic reasons may be recommended [50]. The risk of serious complications (pneumothorax requiring drainage, cardiorespiratory complications during anaesthesia, infection or haemorrhage) not only relates to the invasiveness of the diagnostic procedure itself, but also to the patient's functional status [51]. Subjects eligible for LDCT screening will present themselves mostly with a high comorbidity risk, due to COPD or chronic cardiovascular disease [46, 52].

Adhering to a certified high quality radiology plan for LDCT screening will minimise radiation exposure for screening participants. Further, the adherence to a pulmonary nodule management plan based on nodule diameter, volume and growth rate will help to increase safety for lung cancer screening participants mostly by decreasing the total amount of diagnostic investigations they will need to undergo in order to determine the nature of their screen-detected lung nodules. Moreover, a lower amount of false-positive lesions with a decreased number of additional diagnostic investigations may finally help to decrease participant's anxiety and psychological stress during lung cancer screening [53].

### *Radiation exposure*

The vast majority of lung cancer screening trials were designed more than a decade ago. The LDCT protocols were simply achieved by reducing the fixed tube load of diagnostic CT from typically 100–300 mAs to 10–40 mAs. A CT dose index ($CTDI_{vol}$) of 2–3 mGy was used as a target for NLST [54, 55]. Similar values were used in the NELSON and the various other European trials. The resulting effective dose is roughly 40% of these values for males and 50% for females, resulting in 1–1.3 mSv for a $CTDI_{vol}$ of 2.5 mGy. The organ dose (mSv) to the lung or to the breast can be roughly estimated using $1.5 \times CTDI_{vol}$. Precise numbers vary depending on scanner type, and in particular on the pre-filtering of the X-ray spectrum.


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With recent improvements in detector technology, automated exposure control techniques and iterative image reconstruction, a further substantial decrease in radiation exposure of 80% to a level around 0.2 mSv is possible without impairing image quality [56]. However, radiation exposure will always have to be higher in obese individuals than in normal weight individuals because of the difference in X-ray absorption. Excessive reduction of radiation dose will lead to image quality degradation with either high image noise or loss of image details, which will especially affect sub-solid lesions. These are the limiting factors for further dose reduction.

Radiation risk in the age range of 40 to 60 years is mainly determined by the organ dose to the lungs. Apart from the breast in premenopausal women, other organs have a much lower contribution to excess cancer risk [57]. Radiation exposure and smoking appear to have an additive effect on cancer risk [58]. This means that the excess risk for developing radiation-induced lung cancer may be twice as high in smokers as in never-smokers [59].

Given an effective dose of 1.3 mSv for women and 1.0 mSv for men, the excess lifetime cancer risk was estimated to be 0.02% in male smokers and 0.05% in female smokers if three yearly screening rounds were performed [60]. Risks did not change whether the starting age for screening was 30, 40 or 50 years. This implies that radiation risk becomes important only if the pre-test risk for lung cancer is small. Given a baseline cancer risk of 0.8–2.2% in the various screening trials, the risk–benefit ratio is very favourable. Even if the number of screening examinations increases from three to 24, the excess lifetime cancer risk induced by radiation remains below the baseline cancer risk, but it increases with age [38].

Radiation risk grows strongly if follow-up scans are performed using standard clinical protocols (old equipment 4–18 mSv, new equipment 2–4 mSv [61]) instead of screening with LDCT settings (new equipment 0.2 mSv [56]). For this reason, the work-ups of screen-detected nodules should remain within the screening programme as long as possible [62].

### *Cost effectiveness*

The cost-effectiveness of the screening intervention is one of the major considerations for those who are responsible for screening guidelines, practice measures and insurance coverage [63]. Varying results on the cost-effectiveness of lung cancer screening have been reported [64–67]. In their recent publication, the NLST reports reasonable cost-effectiveness of LDCT screening of lung cancer [68]. LDCT screening as performed in the NLST trial costs $81 000 per quality-adjusted life year (QALY) gained (95% CI $52 000–186 000). Screening trials that cost less than $100 000 per QALY are considered cost-effective. Incremental cost effectiveness ratio (ICER) is the ratio of the change in costs to incremental benefits of a therapeutic intervention or treatment [69]. The NLST ICER was $52 000 (95% CI $34 000–106 000). However, the ICER results of the NLST were highly sensitive to base-case assumptions. For example, if the reduction in mortality from causes other than lung cancer was included in the calculation, the QALY fell down to $54 000. QALY increased to more than $100 000 when the cost of future care was increased. Moreover, estimated cost-effectiveness varied in the subgroup analysis. Screening with LDCT was much more cost-effective in women than in men and among the groups with a higher risk of lung cancer. Whether screening performed in different countries in Europe will be cost-effective depends on exactly how the screening will become implemented [68] and on which respective cost structures and reimbursement policies will be used.

### *Expectation management*

Expectation management is crucial for a successful CT screening programme. It is important for three main reasons: 1) giving participants the ability to understand the benefits and potential harms, 2) reducing anxiety in case a nodule is found and 3) reducing litigation and its chances for success. Screening is very likely to reduce a participant's risk of dying from lung cancer. However, a substantial group of participants will still die from lung cancer. Most cancers found will be in a treatable stage (60–80% stage I) – but not all [8, 70]. Some cancers may grow so slowly that they will not be life-limiting and treating them may be unnecessary (overdiagnosis) [39]. Screening is known to miss nodules present on LDCT [71]. The annual screening programme will pick up nodules missed on earlier scans, which reduces the risk of missed nodules developing into untreatable cancer. As small nodules are extremely common, it is very likely that a nodule will be found. LDCT is not optimally suited for the detection and diagnosis of many other chest diseases. However, incidental findings leading to unnecessary work-up, costs and complications may occur.

Information given to participants, clinicians not involved in screening and the public should be clearly understandable. Informed consent is important because of the dangers of undetected cancers, overdiagnosis or complications due to work-up or treatment of screen-detected lesions. The participants should be aware of the incidental finding policy of the screening programme.

## Broaden the scope

CT-based screening can provide a more global approach of a smoker's lung and associated comorbidities, which are associated with poor health status and prognosis [72, 73]. Regarding smoker's lung features, namely airway disease and emphysema, they can be easily depicted and categorised according to the proposed CT phenotypes [74]. In addition, it is also possible to detect interstitial lung abnormalities in cigarette smokers, as recently observed in 8% of the COPDGene cohort (194 out of 2416) [75]. While such abnormalities are visually assessed, recent approaches favour automated extraction and quantification of morphological changes in order to refine COPD phenotyping [76] and help predict clinical impairment [77].

Smokers have a highly increased risk for the development of cardiovascular diseases, which also coexist with COPD [72]. Since lung cancer screening examinations use non-contrast and non-ECG-gated acquisitions, precise analysis of mural changes at the level of coronary arteries, as well as thoracic aorta, remains beyond the scope of such examinations. However, several studies have documented the feasibility of an imaging approach combining lung cancer and quantification of coronary artery calcium in a single chest CT study [78, 79]. Quantification of coronary and aortic calcium volumes in lung cancer screening CT images has recently been shown to help predict cardiovascular risk. Such an approach might prove useful in the reduction of cardiovascular morbidity and mortality and may enhance the cost-effectiveness of CT-based screening in heavy smokers [80]. Other key targets such as calcifications at the level of heart valves and/or supra-aortic arteries could also be included. Osteoporosis is also increasingly recognised as a major comorbidity which can be picked up on LDCT of the chest.

The specificity of a screening programme might also be increased by including non-imaging, non-invasive biomarkers to allow a better discrimination between benign *versus* malignant conditions. Examination of serum and plasma biomarkers shows some evidence supporting the rationale of using these biomarkers for risk stratification of screen-detected lung nodules [81–83]. However, there are only few biomarkers which could be implemented immediately. We encourage the community to further investigate in this area and define it as an urgent unmet need in the field of lung cancer.

## Suggestions

The European Society of Radiology and the European Respiratory Society are recommending lung cancer screening in comprehensive, quality-assured programmes within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres. Based on the results and experience of completed and on-going lung cancer screening activities, we suggest the following minimum requirements for the implementation of lung cancer screening:

- Accredited medical centres with multidisciplinary expertise and access to trained professionals, including, as a minimum, radiologists, pulmonologists, oncologists, pathologists and chest surgeons.
- Strong smoking cessation programme and experienced staff providing effective cessation and long term abstinence advice.
- Longitudinal comprehensive screening programme throughout the age interval of eligibility, covering the complete protocol, including work-up, follow-up and potential re-entry, also offering an appropriate expectation management. Single-round screening is discouraged.
- Inclusion criteria: age between 55 and 80 years, tobacco smoking history of at least 30 pack-years, and current smoker or ex-smoker who has quit smoking within the last 15 years.
- Exclusion criteria: comorbidities precluding curative therapy and lack of consent to undergo curative therapy.
- Standardised operating procedures for image acquisition, nodule evaluation, positive screening results and their management, monitoring of false-positive results and rate of iatrogenic complications, and appropriate follow-up.
- Computer-assisted nodule evaluation and documentation. Identical measurement software is required for the follow-up. Volumetric measurements are preferred over diameter measurements.
- Multidetector LDCT with at least 16 detector rows providing isotropic high spatial resolution (slice thickness of about 1 mm with an increment of 0.7 mm) and an effective dose between 1 mSv for normal sized individuals and not more than 3 mSv for obese individuals.
- Collection and submission of lung cancer screening data to a lung cancer screening registry. The set-up of a European lung cancer screening registry including biobank and image bank is encouraged.

We also recommend the implementation of the following measures in order to increase quality, outcome and cost-effectiveness of lung cancer screening:

- To increase the pre-test probability by using a risk model and considering additional risk factors.
- To reduce the effective radiation dose to less than 1 mSv per CT examination for all participants.


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- To use volumetric measurements for the assessment of growth rate (tumour doubling time) in order to reduce the rate of false-positives.
- To use computer-assisted systems for automated detection, optimised measurements and follow-up, providing structured reports on nodule volume, localisation, phenotype and standard operating procedure-based suggestions for further management plan.
- To adapt screening intervals based on refined risk models.
- To include additional CT findings such as COPD and vascular calcification.
- To include and study biomarkers to better define screening subgroups and refine nodule management.

## Conclusion

Lung cancer is a devastating disease with poor survival once the disease is advanced. As the main risk factor for lung cancer is smoking, there is an urgent need to advocate against smoking and encourage cessation. There are accumulated data supporting the survival benefit for screening of individuals at high risk for early detection of lung cancer using LDCT. Based on the available evidence, we summarised the key elements necessary for a comprehensive lung cancer screening programme in Europe including minimum requirements and recommended refinements. These should be adjusted to the national infrastructure and healthcare system in order to exactly define eligibility using a risk model, nodule management and quality assurance plan. The establishment of a central registry, including a biobank and an image bank, preferably on a European level, is strongly encouraged.

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