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ESR/ERS statement paper on lung cancer screening

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Abstract

In Europe, lung cancer ranks third among the most common cancers, remaining the biggest killer. Since the publication of the first European Society of Radiology and European Respiratory Society joint white paper on lung cancer screening (LCS) in 2015, many new findings have been published and discussions have increased considerably. Thus, this updated expert opinion represents a narrative, non-systematic review of the evidence from LCS trials and description of the current practice of LCS as well as aspects that have not received adequate attention until now. Reaching out to the potential participants (persons at high risk), optimal communication and shared decision-making will be key starting points. Furthermore, standards for infrastructure, pathways and quality assurance are pivotal, including promoting tobacco cessation, benefits and harms, overdiagnosis, quality, minimum radiation exposure, definition of management of positive screen results and incidental findings linked to respective actions as well as cost-effectiveness. This requires a multidisciplinary team with experts from pulmonology and radiology as well as thoracic oncologists, thoracic surgeons, pathologists, family doctors, patient representatives and others. The ESR and ERS agree that Europe's health systems need to adapt to allow citizens to benefit from organised pathways, rather than unsupervised initiatives, to allow early diagnosis of lung cancer and reduce the mortality rate. Now is the time to set up and conduct demonstration programmes focusing, among other points, on methodology, standardisation, tobacco cessation, education on healthy lifestyle, cost-effectiveness and a central registry.

Key Points

- *Pulmonologists and radiologists both have key roles in the set up of multidisciplinary LCS teams with experts from many other fields.*
- *Pulmonologists identify people eligible for LCS, reach out to family doctors, share the decision-making process and promote tobacco cessation.*

The ESR and ERS agree that Europe's healthcare systems need to allow citizens to benefit from organised pathways to early diagnosis and reduction of mortality of lung cancer. Now is the time to set up and implement large-scale programmes. http://bit.ly/2miF0cO

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- *Radiologists ensure appropriate image quality, minimum dose and a standardised reading/reporting algorithm, together with a clear definition of a "positive screen".*
- *Strict algorithms define the exact management of screen-detected nodules and incidental findings.*
- *For LCS to be (cost-)effective, it has to target a population defined by risk prediction models.*

Keywords Early detection of cancer · Tobacco use cessation · Lung neoplasms · Carcinoma, bronchogenic · Cost-benefit analysis

Introduction

In Europe, lung cancer ranks third among the most common cancers; however, it remains the biggest killer [1]. Recent European cancer mortality projections predict a downward trend in most cancer types in both sexes owing to better prevention and treatment, with the exception that lung cancer mortality is expected to rise in women [2]. Worldwide, tobacco use is the single greatest avoidable risk factor for lung cancer mortality. Integrated preventative action across the lifespan, combining both primary and secondary prevention, is needed. Implementing comprehensive tobacco control policies is paramount in tackling tobacco uptake by young people, which leads to premature mortality. Nevertheless, policies require time to show their results. In the short term, promoting tobacco cessation among current smokers and screening high-risk ever- and former smokers will have a higher impact in reducing tobacco-related mortality [3].

Since the publication of the first European Society of Radiology (ESR) and European Respiratory Society (ERS) joint white paper on lung cancer screening (LCS) [4], many new findings have been published in the field and discussions regarding implementation of LCS in the scientific arena, healthcare community and general public, as well as among policymakers, have advanced considerably. Thus, the ESR and ERS concluded that an update to the statement paper was required to take into account recent developments in the field as European nations begin to consider LCS implementation.

Methodology

A joint task force (TF) with members of the ESR and the ERS was established in December 2017. The TF consisted of 22 members from multiple disciplines and European countries. All members of the TF disclosed their conflicts of interest before initiation of the project. After discussions, the TF decided to focus on recent developments in LCS and nine chapter groups were formed. Each group consisted of between two and five TF members. Each group conducted their own literature searches on their respective subjects on at least one database (usually Medline) using relevant keywords in spring or summer 2018. Depending on the subject of interest, some groups did not restrict the timespan of their searches, while others did, most often looking at studies published from 2000 onwards. Each group screened the identified studies and selected the ones to include in this statement. The TF members focused primarily on studies published in English. Randomised controlled trials (RCTs), large cohort studies, guidelines and systematic reviews were selected. This statement provides a narrative, non-systematic review of the evidence and description of the current practice in LCS as well as of aspects that have not received adequate attention until now. It is not based on a systematic literature review and grading of the evidence and is instead a statement on pivotal points to consider in LCS. Therefore, it does not provide recommendations for clinical practice. The TF held regular telephone conferences, during which each chapter was discussed and commented upon. The final version of the manuscript was reviewed and approved by all TF members.

Participants' involvement

The success and effectiveness of screening programmes strongly depends on the proportion of at-risk population engaged into the programme. Therefore, the information has to be accessible and well targeted, both to the public and potential participants of LCS. Explanations around the benefits and harms of LCS are important, e.g. risk of radiation exposure when having a computed tomography (CT) scan. For LCS to be successfully implemented, specific explanation is required regarding the difference between low-dose and standard diagnostic scans and their respective potential risks. The different perceptions of the "outcome" for a LCS health service programme and the individual are important, and need to be conveyed through health campaigns and by training healthcare professionals to increase patient education and engagement in LCS using a patient-centred approach. Detecting other abnormalities (incidental findings) as a result of LCS could be viewed as an additional benefit from a screening programme. However, this could also cause anxiety (e.g. scanxiety) and mental health issues for some individuals [5, 6].

There is a stigma attached to tobacco and lung cancer: the perception that it is a self-induced disease may undermine access to healthcare, preventing individuals from seeking screening or healthcare services. Highlighting the tobacco industry and its commercial activities as the driver of the

tobacco epidemic could be an effective strategy to reduce the stigma of "smokers' behaviour" into lung cancer causality [7]. A large survey of public interest in LCS in England underlined these concerns by concluding that minimising stigma related to cancer risk in smokers was crucial to improving participation [5]. For example, in the UK, the term "lung health check" is being used to promote a positive view of screening in order to encourage participant recruitment [8].

To reach those most likely to benefit from LCS, consideration must be given to persons with low levels of either literacy and/or health literacy who are among those often at highest risk of lung cancer. The clear language and terminology used in linking lung screening and tobacco cessation should be reflected in the native language, incorporating regional variations and attitudes. It is important to ensure that information about the screening process is co-designed with patients, the public and experts. Health literacy and how it is addressed will be key to the uptake of screening in hard-to-reach populations. Qualitative research, involving a low-income, racially diverse patient group, demonstrated that these groups were not aware of the purpose of LCS; they wanted to know more about the potential harms and benefits, and wanted effective and tailored communication from their medical team to enable them to make decisions about screening [9]. Any screening programme will need to think about its approach to men and women, because men are generally less likely to seek direct health interventions. Tobacco cessation counselling and support should also contemplate a sex-based approach. It is very important to ensure systems are in place so that people taking part in LCS are reassured that they will be followed-up in a timely way and cared for as required.

The decision to be screened or not and decisions on any future procedures should be made using a shared decision-making (SDM) process [10]. A collaborative process between healthcare providers and screening participants allows decisions to be made together while incorporating the available best evidence and recommendations. SDM includes discussion of different aspects of LCS, e.g. benefits, harms, follow-up diagnostic testing, known and unknown risks of additional testing associated with incidental findings, false-positive rate, overdiagnosis and radiation exposure. Furthermore, it should provide counselling on the importance of adherence to the programme, impact of comorbidities, ability or willingness to undergo diagnosis and treatment, maintaining tobacco abstinence or information about tobacco cessation services, and pertinent patient values and preferences [11]. However, the issues to be considered are complex and members of the public may vary in the level at which they would like to be involved in the decisions. Nowadays, evidence-based, patient-centred SDM should be the standard care. Following the model developed by Politi et al. [12], patient-centred SDM should follow a systematic structured approach (Table 1). According to oncology practice, using decision aids may provide structured approaches to communicate knowledge, elicit patient values and clarify their preferences, and engage them with the plan for the next steps in decision-making [12]. These tools involve consultation planning, question prompt lists, decision boards, telephone visits, videos and multimedia, but require adequate planning and engagement of a multidisciplinary team [11, 12]. Additionally, effective communication between the primary care and other providers who refer participants and the LCS team will be crucial to ensure high-quality patient-centred SDM. Decision support tools in different formats can help foster deliberation, but should be used as an integral part of the SDM process and not used as stand-alone tools [11, 13].

Overview of LCS activities in Europe

To date, there are no nationally organised LCS programmes worldwide although there is a high level of evidence in favour of this strategy [14–16]. The US Preventive Service Taskforce and the National Comprehensive Cancer Network have issued guidelines recommending LCS in a high-risk group of (ex-)smokers [17, 18]. The Centers for Medicare and Medicaid Services (the coverage body of Medicare) covers low-dose CT (LDCT) for the purpose of LCS in individuals with the following criteria: age 55–77 years, history of ≥30 pack-years of smoking, and current smoker or former smoker with <15 years since quitting.

In China, cancer screening is organised as a demonstration project in various provinces for highly prevalent cancer types, including lung [16]. Other trials and pilot projects are underway in developed countries worldwide, including Australia, Brazil, Canada, Japan and South Korea.

Table 1 The five steps in shared decision-making

1	Acknowledge the importance of shared decision-making in healthcare and engage participants
2	Discuss in a balanced way the potential harms, benefits and uncertainty
3	Acknowledge the clinical situation and different options to every participant
4	Elicit participants' preferences and values
5	Agree on a plan for the next steps in the decision-making process

Adapted from Politi et al [12]

There is currently no organised nationwide LCS in Europe. Opportunistic screening is available as a private service in some countries and in some cases is even covered by some regional insurance companies. The current status of LCS in individual European countries is presented in Supplementary Appendix I.

The largest European trial is the Dutch–Belgian NELSON trial (Nederlands-Leuvens Longkanker Screenings Onderzoek) involving 7900 participants in the CT screening arm and 7892 participants in the control arm [19]. Preliminary data (only reported as a congress abstract and not yet published) on mortality showed a lung cancer-specific mortality reduction with LCS of 26% in men and up to 61% in women at high risk of lung cancer after 10 years [15]. In females at high risk, this figure ranged from 39% to 61% after 8 and 10 years respectively [15]. Lung cancer mortality reduction is therefore higher in NELSON than in the National Lung Screening Trial (NLST) [14] and the primary endpoint of the study has been met. The results for all-cause mortality were less favourable, with a reduction of 3.2% as compared to 6.7% for the NLST. Currently, there are a number of ongoing early lung cancer detection pilot projects in the UK using LDCT [20]. In other countries, pilot studies are in preparation; indeed, Poland has organised a national demonstration programme [21]. Implementation of LCS is being discussed throughout Europe among clinicians and policymakers. Items such as balance of benefit and harms, cost-efficiency, SDM, integration of tobacco cessation, service implementation and participation rate still have to be ironed out. A recent scientific seminar of the ERS was devoted to this effort.

Participation in LCS trials

The effectiveness of screening, shown as the rate of prevented deaths as well as its cost-effectiveness, increases with the population's risk of lung cancer. Within the population studied in the NLST (current and former smokers, >30 pack-years, aged between 55 and 75 years) [14], significant discrepancies were shown in prevented lung cancer deaths: the numbers needed to screen to prevent death from lung cancer were lower in the higher-risk group and 88% of CT-prevented lung cancer deaths occurred in these very high-risk individuals, who represented 60% of participants; conversely, 20% of participants at lowest risk accounted for only 1% of CT-prevented lung cancer deaths [22, 23]. The risk of lung cancer is associated with not only smoking history and age, but also factors such as family history of lung cancer and (occupational) exposure to asbestos, radon, *etc*. Therefore, proper selection of participants in LCS trials has emerged as a significant area for improvement. The application of risk prediction models could result in the selection of individuals with increased pre-test probability, thus increasing screening effectiveness. Several risk prediction models have been developed for this purpose, such as the two-stage clonal expansion (TSCE) model for lung cancer incidence and death [24], the Liverpool Lung Project (LLP) model [25], the Knoke model [26], the Bach model [27] and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Model 2012 ($PLCO_{M2012}$) [28]. The TSCE and Knoke models examine age, sex and smoking-related characteristics as risk factors, while the Bach model also considers asbestos exposure as a risk factor. The LLP model is more complex and includes age, sex, smoking duration, personal and family history of cancer (in particular, cancer before the age of 60 years), personal history of pneumonia, and asbestos exposure as risk factors. The $PLCO_{M2012}$ 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 (Table 2) [22, 24–27, 29]. Among the existing risk prediction models there are discrepancies regarding predictive performance. The $PLCO_{M2012}$, Bach and TSCE incidence models have been shown to be more sensitive than the NLST criteria in predicting 6-year lung cancer incidence in the prostate, lung, colorectal and ovarian chest X-ray arm [30]. There is also evidence in favour of the $PLCO_{M2012}$ in terms of greater sensitivity, positive predictive value for lung cancer detection and cost-effectiveness [28].

While application of validated risk prediction models may represent an acceptable approach to optimally selected populations at high risk, there are issues regarding their incorporation in LCS trials. First, evidence of their superiority comes mainly from retrospective or micro-simulation modelling analyses. The LLP risk was used prospectively in the UK Lung Screen trial [31]; however, data from more prospective studies would further support their standard use [32]. Furthermore, application of risk prediction models could lead to excessive inclusion of older individuals with more comorbidities who would not benefit from screening. Conversely, NLST criteria include an important number of low-risk individuals who are also unlikely to benefit from screening. A recent publication simulates the benefits and harms of LDCT scans from 2016 to 2030 in the US population and projects the number of lung cancer deaths for the 15-year period: the authors estimate a reduction in lung cancer mortality of 3.5% from the initial 20% seen in the NLST trial. However, this estimation derives from the overall study population, including those ineligible for screening under the Centers for Medicare and Medicaid Services guidelines and the non-adherent individuals [33]. Excessive complexity may also become an issue when such models are applied in clinical practice, though this may be mitigated by information technology solutions. Selection of the optimal risk threshold and validation in a real-world setting should also be addressed by ongoing research.

Two further relevant questions about screening include the search for optimal intensity and duration of screening. Currently, there is major evidence for annual intensity from

Table 2 Summary of risk prediction models

Risk factors	Models				
	TSCE [24]	LLP [153, 154]	Knoke [26]	Bach [27]	$PLCO_{M2012}$ [28]
Age	✓	✓	✓	✓	✓
Sex	✓	✓		✓	
Smoking status	✓	✓	✓		
Smoking duration	✓	✓	✓	✓	✓
Smoking intensity	✓		✓	✓	✓
Type of cigarette smoked		✓			
Age at smoking start and end		✓			
Years since cessation	✓		✓	✓	✓
Race					✓
Education					✓
BMI					✓
COPD		✓			✓
Personal history of cancer		✓			✓
Family history of lung cancer		✓			✓
Personal history of pneumonia		✓			
Asbestos exposure		✓		✓	

TSCE, Two-Stage Clonal Expansion; *LLP*, Liverpool Lung Project Risk; *$PLCO_{M2012}$*, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Model 2012; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease

NLST. It remains unclear whether annual screens are needed for all high-risk individuals [34]. Results from the European trials, NELSON and Multicentric Italian Lung Detection (MILD), showed that lower-intensity screening algorithms did not hamper long-term survival [15, 35]. Still, the 2.5-year timeframe in the fourth round of NELSON resulted in a significant increase in interval cancers and more cancers detected at a later stage [36]. Blood and breath biomarkers may have a role in a more risk-stratified approach and in tailoring the most beneficial LCS protocol; however, there is no current evidence to support their utility in screening [37].

The duration of LCS was modelled to cover over two decades, after the age of 55 years [38]. This led international authorities to suggest prolonged screening in high-risk individuals [17, 39–41]. Still, the National Comprehensive Cancer Network underscores that there is uncertainty about the appropriate duration of screening and the age at which screening should be withdrawn [40]. Data from prospective trials confirmed and reinforced the indication for prolonged screening. Two long-term trials, NELSON (5.5 years) and MILD (>6 years), showed an exceptional reduction in lung cancer mortality [15, 35], which outperformed the 20% reduction reported after three annual rounds of the NLST, although both NELSON and MILD did address smaller and relatively lower risk populations than did the NLST. The MILD trial specifically investigated the dynamics of prolonged LCS by setting a landmark analysis beyond 5 years, which showed a 58% reduction in lung cancer mortality and 32% reduction in overall mortality. These results suggest that prolonged screening yields cumulative advantages and, therefore, support the indication for screening to cover the whole age range of high-risk populations [42].

Europe still has the highest prevalence of tobacco use [43], which is particularly high among females, while male smoking has recently passed its apex. Taking into account a time lag of around 30–40 years between the peak of smoking prevalence and the peak of lung cancer mortality [44], the necessity for early detection of lung cancer is especially high in the EU population. Even if tobacco prevalence decreases, such as is anticipated in the USA, high tobacco use persists among socially disadvantaged people [45], and the effects of emergent products, such as e-cigarettes and heated tobacco, and air pollution remain unclear.

Tobacco cessation

Tobacco is the main cause of lung cancer. Over time, changes in tobacco manufacturing have significantly increased lung cancer risk among smokers, despite current smokers smoking fewer and filtered cigarettes [46]. Smokers, especially those more dependent and socially disadvantaged, neglect their cancer risk and report false health beliefs [47]. While LCS can lower lung cancer mortality [14, 15], tobacco cessation remains the most important intervention to decrease lung cancer risk and premature mortality, and improve health, even among long-term or older smokers [46, 48]. Tobacco cessation also

improves lung cancer prognosis and survival and is associated with better clinical outcomes to treatment [48].

Most smokers contemplate quitting; however, they express concerns and low self-confidence in stopping smoking, especially long-term and more dependent smokers [46, 49]. While 50% of the participants undergoing LCS are current smokers [14], tobacco cessation care is mostly neglected and cessation research is scarce in LCS settings [50].

Motivation to quit among participants undergoing LCS varies according to different study populations: among smokers in the NELSON trial, 41% reported no intention to quit [51] compared to 13% in the NLST [52]. Several studies report that many smokers undergoing LCS are motivated to quit and are interested in receiving cessation care, suggesting that screening may provide an opportunity to deliver cessation treatment among high-risk smokers who may be particularly responsive [50, 53]. The main findings of RCTs and observational studies evaluating the effect of LCS on tobacco cessation are provided in Supplementary Appendix II. Even though these studies have important limitations, most report higher motivation to quit and higher cessation rates among participants compared to the general population. Furthermore, a positive or indeterminate screening finding seems to prompt cessation and decrease smoking relapse rate [54]. However, while participating in a LCS study seems to enhance cessation [55], RCTs failed to demonstrate higher cessation rates in the intervention arm in comparison to the control group [51]. Finally, long-term follow-up studies of LCS participants contradict the wide concern that negative screening results may reinforce smoking [56]. There is some evidence that neither screening itself nor its combination with low-intensity/non-tailored counselling consistently promotes abstinence among smokers undergoing LCS [57]. By contrast, the few studies that investigated the impact of supporting smokers undergoing LCS with more comprehensive cessation support suggest that intensive interventions may be effective in fostering abstinence [54, 57]. A secondary analysis of the NLCT reports that sustained tobacco abstinence in the controls reduced lung cancer-specific mortality similarly to screening (20%). Furthermore, sustained abstinence and screening lowered mortality by 38% [58].

Pairing LCS with evidence-based tobacco cessation will favour the balance between screening benefits and harms and increase its cost-effectiveness. Further research is needed to evaluate effective and tailored behavioural strategies for targeting high-risk smokers, the timing for delivering the interventions and how to engage and train LCS provider teams in cessation advice. Treatment should follow smoking-cessation guidelines and be tailored to participants' socio-demographics, smoking behaviour and health beliefs [50]. The LCS provider team should be trained to deliver evidence-based tobacco cessation brief advice (5A's/5R's model) and refer motivated smokers to cessation programmes [50, 59].

State-of-the-art algorithms in LCS

The prerequisite to all nodule management algorithms is a CT protocol, ensuring sufficient diagnostic quality to allow for volumetric evaluation while keeping the radiation dose as low as reasonably achievable. In the NLST, the projected cumulative radiation dose in three screening rounds was 4.5 mSv. However, additional diagnostic CT scans to evaluate suspicious CT findings and positron emission tomography (PET)-CT scans led to an estimated median radiation dose per participant over 3 years of 8 mSv [60]. Based on NLST data, it has been estimated that LCS may lead to one radiation-induced cancer in 2500 participants [60]. Modern CT scanners provide high-resolution, low-noise images for accurate detection and measurability of nodules at ultra-low dose, e.g. well below 1 mSv [61, 62], thus substantially decreasing the risk of radiation-induced cancer. The reading protocol should target two objectives: first, to avoid misdetection; and second, to leave out insignificant findings. Defining the number and expertise of readers and support tools, including computer-assisted decision (CAD) and volumetry software and advanced artificial intelligence (AI) algorithms, is therefore required.

Expertise in lung cancer CT reading plays an important role in distinguishing non-nodular opacities, scars, atelectasis, intrapulmonary lymph nodes or fat-containing hamartomas from typically malignant nodules. Besides size, the density of nodules has an impact on management strategies. Subsolid nodules have a better prognosis than solid nodules and are thus managed less aggressively [63, 64]. Sub-solid nodules may correspond to pre-invasive or early invasive adenocarcinomas, which grow very slowly [65]. Very small (<5 mm) pure ground-glass nodules frequently correspond to an atypical adenomatous hyperplasia, which is a premalignant lesion.

To date, few radiologists are trained for LCS. Education, training, certification and quality assurance of reading radiologists is warranted, notably to avoid overcalling, which might result in over-investigation of minor findings or overtreatment of findings that can be controlled by active surveillance [66, 67]. A LCS certification programme has been prepared by the European Society of Thoracic Imaging, based on e-learning and workshops and validated by a final examination, in order to train radiologists in the specific task of LCS (www.myesti.org).

Because detection errors still occur for nodules that are clearly visible in retrospect, most screening studies had a double reading of CT, NLST being an exception [19, 31, 65, 68–70]. A paper from the NELSON group [71] reported 78% sensitivity for nodule detection with double reading

and 96.7% with CAD. Excluding nodules <5 mm reduced false-positive detections to an acceptable mean number of 1.9 per examination. Moreover, the MILD group specifically addressed sub-solid nodules identified by CAD, and reported that the software had a sensitivity of 88.4% [72]. Therefore, it has become clear that CAD can increase the efficiency of LCS reading and should be implemented. However, a recent study [73] concluded that older software systems fail to flag a substantial number of cancerous lesions and have a fairly high false-positive rate. CAD algorithms based on deep learning, in particular convolutional neural networks, i.e. AI, have higher sensitivity and lower false-positive rates [74]. Similar deep learning algorithms have been successful not only in the characterisation of nodules as solid or sub-solid (part-solid or ground-glass) with an accuracy comparable to radiologists [75], but also in estimating the probability of malignancy of nodules [76]. Although size and growth are the most important discriminators for malignancy [64], morphologic assessment such as spiculation, nodule location and nodule shape should also be taken into account [77, 78]. Furthermore, perifissural nodules, which correspond to intrapulmonary lymph nodes, require a less aggressive approach [79, 80]. Knowledge of early lung cancer morphology and uncommon manifestations is vital given that these lesions may go unnoticed by CAD systems [81, 82].

Thorough validation studies are now needed to investigate the performance of the best deep learning, CAD and volumetry systems, and how such systems can be best implemented in a LCS setting. Possibilities include the use of AI software as a second, concurrent or first reader, or even as a stand-alone solution for a fraction of the cases if superior performance to expert radiologists is confirmed. It is therefore expected that clinical implementation of AI will boost the efficiency of LDCT reading in LCS, both in detecting and interpreting nodules and density. Further work is needed on translating superior AI performance into clinical decision-making.

There have been different definitions of a positive screen result, resulting in different management guidelines (Table 3). Some are based on nodule diameter and others on volumetry. In an effort to standardise the interpretation, reporting and recommendations for the management of pulmonary nodules in LDCT screening, the American College of Radiology established the Lung-RADS classification (Lung CT Screening Reporting And Data System) with management guidelines based on diameter [83]. While threshold size for solid nodules was ≥4 mm in the NLST (longest diameter), Lung-RADS used ≥6 mm for solid nodules at baseline [14]. In contrast to the NLST, in the Lung-RADS mean diameter is calculated by measuring the long and short axis to one decimal point and mean nodule diameter is reported to one decimal point. This change in threshold led to a decrease in false-positive rate, but also resulted in reduced sensitivity on a retrospective assessment of NLST data [84]. Under International

Table 3 State-of-the-art definitions of positive screens at baseline

	Positive			Indeterminate			Negative		
	Solid	Part-solid[#]	Non-solid	Solid	Part-solid[#]	Non-solid	Solid	Part-solid[#]	Non-solid
Lung-RADS	≥8 mm	≥6 mm	–	6–<8 mm	<6 mm	≥30 mm	<6 mm[+]		<30 mm
BTS	≥300 mm^3 and Brock ≥10%	–	–	≥300 mm^3 and Brock <10%	≥5 mm	<80 mm^3			
				80–<300 mm^3			<5 mm		
EUPS	≥300 mm^3	–	–	100–<300 mm^3	≥5 mm	<100 mm^3	<5 mm		
NCCN	8 mm	≥6 mm		6–7 mm	≥6 mm	≥20 mm		≤5 mm	≤19 mm
I-ELCAP	≥15 mm	6–14.9 mm[¶]		<6 mm or 6–14.9 mm[+]	<6 mm or 6–14.9 mm[+]	Any size	No non-calcified nodules		

Lung-RADS, Lung CT Screening Reporting And Data System; *BTS*, British Thoracic Society; *EUPS*, European Union Position Statement on Lung Cancer Screening; *NCCN*, National Comprehensive Cancer Network; *I-ELCAP*, International Early Lung Cancer Action Program. [#]: may refer to size of the solid component; [¶]: long and short axis should be measured to one decimal point and mean nodule diameter should be reported (also to one decimal point); [+]: total diameter

Early Lung Cancer Action Program criteria, nodule management also depends on nodule diameter with a positive screen result for solid nodules ≥15 mm or smaller nodules (6–14.9 mm) demonstrating malignant growth at 3 months [85].

European screening programmes have used another approach, based on volumetry, in order to overcome the limitations of two-dimensional measurements, which include large intra- and inter-reader variability [86]. The NELSON study defined non-calcified solid nodules as positive screens if they had a volume >500 mm^3 or nodules with a volume of 50–≤500 mm^3 and a 25% increase in volume at a 3-month follow-up [87]. Current nodule management protocols for volumetric measurement are based on data from the NELSON trial [88].

The British Thoracic Society guidelines recommend risk assessment of nodules >8 mm or >300 mm^3 using the Brock model. Nodules with ≥10% risk of malignancy are then referred for PET-CT with further risk assessment using the Herder model [63].

Of particular concern is the incidence of solid nodules that were missed on a previous scan or developed in the interval between screening rounds. With an annual incidence of 3%–13%, these nodules are not uncommon and turn out to be lung cancer in 6% of participants, thus exhibiting a greater risk of malignancy with smaller size compared to baseline nodules [77, 89], whereas incidence nodules found during very short-term follow-up (*e.g.* 3 months) are more likely to be inflammatory. They require a different management strategy than solid nodules detected at baseline [89, 90]. While data on incidence of sub-solid nodules are limited, they show that such lesions, when persistent, have a more indolent course, justifying follow-up [91].

One accomplished goal of LCS is to identify lung cancer in its early stages, especially stage 1A (Table 4), because these patients will have the highest chance of successful treatment, with definitive surgery being the treatment of choice. Less invasive procedures, such as video-assisted thoracoscopic surgery, which can be effective, safe and have fewer negative long-term impacts on the patient's overall health status, might become increasingly important. Consequently, surgical procedures for lung resection need to be re-evaluated in terms of oncological outcomes as well as post-operative complications (Supplementary Appendix III).

Quality assurance and performing standards should be integrated in any LCS to optimise the benefits of screening and minimise the potential risks. Continuous monitoring and periodic evaluation permit modification and optimisation of the screening programme. Quality assurance should be performed at institutional and individual level, at all steps of implementation, including technical aspects of LDCT, scan procedure, radiation dose, scanner performance, reader performance, false-positive rate, recall rate and negative predictive value. In this regard, structured reporting and centralised data registration are mandatory. Quality assurance for all diagnostic and/or therapeutic steps after a positive screen is strongly advised. European Society of Thoracic Imaging is working on a comprehensive structured report that includes demographics, technical details of LDCT acquisition and nodule characterisation through major international guidelines. This document will be made publicly available with the aim of providing a standard for data collection and continuous quality assurance.

Overdiagnosis and harms

Overdiagnosis in cancer screening is defined as over-detection of an indolent pathology that would not otherwise have become clinically apparent [92]. Overdiagnosis is conspicuous in cancer screening, which can identify precancerous and neoplastic pathology in asymptomatic subjects. A reduction of overdiagnosis is an important aim for all LCS programmes, to avoid overtreatment and its potential morbidity and mortality [93]. The estimate of overdiagnosis is prone to bias [93] because it is linked to a pathological reference standard [94]. Thereby, several metrics become altered, including diagnostic test accuracy, incidence and prevalence, stage shift and survival rates [95]. The degree of overdiagnosis should be accounted for when using risk models and estimating outcomes.

The rate of overdiagnosis in the NLST was estimated to be ~20% for screen-detected cancers and ~80% for screen-detected lepidic adenocarcinoma [96]. However, the NLST was not designed to estimate the degree of overdiagnosis due to contamination by chest X-ray in the control group. The Italian Lung Cancer Screening trial (ITALUNG) revealed no overdiagnosis, which indicates that this trial was either biased and/or that CT screening was limited in its ability to detect the earliest-stage lung cancers [97]. The Danish Lung Cancer Screening Trial (DLCST) concluded that 67.2% of screening-detected cancers were overdiagnosed, with little degree of contamination bias but a potential minor uneven distribution at randomisation: more heavy smokers and participants with COPD in the intervention group [98]. The most recent NELSON results did not disclose the estimate of overdiagnosis; however, the cumulative incidences of lung cancer in the intervention and control arms indicated some degree of overdiagnosis [15].

There are two reasons for overdiagnosis in cancer screening: 1) slow or no growth of cancer pathology and 2) competing risk of death [95]. Lung cancer histology with a slow growth rate is more prone to overdiagnosis, notably adenocarcinoma manifesting as a persistent non-solid nodule (NSN) [92]. Moreover, if competing risk of death is high, the risk of overdiagnosis also increases. The European trials showed that either prospective conservative management of NSNs

Table 4 The incidence of early disease (stage IA, IB) across the main randomised LCS trials

Study	Group	Subjects n	Age years	Lung cancer detected by LDCT (% of screened group)[#]	Stage Ia (% of lung cancer detected by LDCT)	Stage Ib (% of lung cancer detected by LDCT)
NELSON [155]	LDCT	7438	50–75	187 (3)		130 (66)
	T0	7135		62	41	3
	T1	6769		53	41	1
	T2	6380		72	48	6
	Control	7907				
ITALung [156]	LDCT		55–69	41[¶]		23 (56)
	T0	1406		18		10 (55)
	T1	1356		2		2 (100)
	T2	1308		9		9 (100)
	T3	1263		6		6 (100)
	Control	1593				
DLCST [157]	LDCT	2052	50–70	69 (3)	37 (53)	10 (14)
	T0	2047			8	1
	T1	1976			4	3
	T2	1944			10	0
	T3	1982			5	2
	T4	1851			10	4
	Control	2052		24 (1)	3 (12)	2 (8)
MILD [105]	LDCT annual	1190	49–75	29 (2.5)	15 (52)	1 (3)
	LDCT biennial	1186		21 (2)	9 (43)	3 (14)
UKLS [158]	LDCT	1994	50–75	42 (2)	26 (62)	2 (4)
	T0			34		
	T1			8		
	Control					
DANTE [159]	LDCT	1264	60–74	66 (5) by screening 38 for other reasons	31 (46)	16 (24)
	Control	1186		72 (6)	6	10
NLST [14]	LDCT		55–74	649 (3.6)	329 (51.8)	71 (11.2)
	T0	26309		270 (3.8)		
	T1	24715		168 (2.4)		
	T2	24102		211 (5.2)		
	CXR			279 (5.5)	90 (32.7)	41 (14.9)
	T0	26035		136 (5.7)		
	T1	24089		65 (4.4)		
	T2	23640		78 (6.6)		

LCS, lung cancer screening; *LDCT*, low-dose computed tomography; *CXR*, chest X-ray. [#]: reported lung cancer detection rates do not reflect equivalent timeframes; [¶]: including six cases of carcinoid and small cell lung cancer that were excluded from the numbers detailed by rounds

[99] or retrospective detection of long-standing NSNs [100] was not associated with increased stage at resection. Extremely rare lymph node metastasis and 100% 5-year survival have been reported for NSNs [101]. For NSNs, size of the solid component (>5 mm), its ratio to total nodule size (≥80%) and its evolution can be used to minimise the rate of overdiagnosis [67, 102].

Potential strategies to reduce overdiagnosis include 1) risk models for multidimensional stratification of participants and nodules [103]; 2) conservative management of sub-solid nodules [99]; 3) quantification of the volume doubling time [104]; and 4) longer interval of screening, which translates into a reduction of LDCTs [105] and eventually a reduction of false-positive findings undergoing referral, thus reducing overtreatment.

Potential unintended harms of medical screening include the psychosocial consequences of false positives and overdiagnosis. If such consequences are to be quantified adequately, measures with high-content validity and adequate psychometric properties are needed [106]. These criteria have recently

been included in a checklist to be used in systematic reviews for which the primary outcome is patient-reported outcome measures (PROMs) [107]. Here, it is emphasised that the "content validity is considered to be the most important measurement property" [107]. If a PROM encompasses scales, then evidence of uni-dimensionality and invariant measurement of these scales should be provided [107]. The ideal design for studies on psychosocial consequences is a RCT with a baseline measurement and no or little attrition. Moreover, the same cohort should be followed in a longitudinal design over months to years so that potential long-term consequences can be measured [108]. However, selection bias might be a problem: participants in the DLCST had a more favourable sociodemographic profile and were more psychologically robust compared to the general population of heavy smokers [109]. Therefore, selection bias could result in the actual psychosocial consequences being underestimated [109]. A study using qualitative interviews in focus groups that psychometrically analysed survey data has revealed that having abnormal and false-positive LCS results can have a wide range of psychosocial consequences that can be adequately quantified with PROMs [110]. One study investigating the first two screening rounds in the DLCST concluded that all participants experienced negative psychosocial consequences, which were worse for the control group [111]. Another study investigating all five of DLCST's screening rounds concluded that these negative psychosocial consequences persisted throughout the trial's 4 years; both the intervention group and the control group reported higher negative consequences compared to the baseline measurement, which again were worse for the control group [112].

Additional and incidental findings: Value and management

In the NLST, there was a reduction in overall mortality in the CT arm of 6.7% [14]. Thus, there may be potential for added value inherent to LDCT focusing on the "big three" killers of lung cancer, COPD (emphysema, bronchial wall thickening) and cardiovascular disease (arteriosclerosis), as well as other smoking-related diseases and comorbidities visible on LDCT, e.g. interstitial lung abnormalities, arteriosclerosis, sarcopenia, osteopenia and aortic aneurysm [113].

With regards COPD and pulmonary emphysema, smokers with airway obstruction have a higher risk for developing lung cancer than smokers without airway obstruction [114]. Severe COPD and fibrosis are associated with very limited life expectancy, even without synchronous development of lung cancer [115]. Almost 10% (175 out of 1865) of all deaths in the CT arm of the NLST were from respiratory illnesses other than lung cancer [14]. A recent study showed that LCS participants with more respiratory abnormalities seen on CT carry a higher risk of dying from respiratory disease [113].

Cardiovascular disease was the leading cause of death in the NLST rather than lung cancer [14]. The presence and burden of coronary artery calcium (CAC) reflected the overall atherosclerotic burden and strongly correlated with the risk of developing cardiovascular events [116]. In clinical practice, CAC is evaluated using a designated ECG-gated CT scan. However, CAC can also be effectively identified and measured using low-dose ungated CT [117].

Heavy smokers are also at an increased risk of bone density loss and consecutive osteoporotic fractures [118], which can easily be visually identified and graded. In a sub-cohort of the NELSON, an association of all-cause mortality with vertebral fractures was identified [119]. In the same study, vertebral bone density measurement using CT attenuation values showed a low but statistically significant negative association with mortality.

Inclusion of such imaging findings into risk prediction models might positively impact the cancer detection rate, survival and, consequently, cost-effectiveness. Thus, the reporting of smoking-related disease in the setting of LCS programmes could be considered. With comprehensive and sophisticated strategies in place, this approach may transform LCS programmes into an attractive prevention programme for high-risk individuals. Further work is required to show whether therapeutic or lifestyle interventions lead to actual benefits for patients following identification of non-lung cancer abnormalities.

Incidental findings in LCS can be defined as findings on thoracic CT unrelated to the primary purpose of identifying lung cancer [120]. Minor and clinically insignificant incidental findings are common on LDCT and can potentially lead to unnecessary investigations, additional costs and patient anxiety. Reported prevalence of incidental findings in the thorax, as well as in adjacent neck or abdominal regions, differs widely among screening trials and a few published routine care studies, with rates from 8% to 94% [121–125]. The most common incidental findings occur in the cardiovascular system, followed by renal, hepatic and pulmonary lesions [122].

Although the American College of Radiology has published white papers on incidental findings in the thorax, pancreas, kidneys, adrenal glands, liver and thyroid gland [125–129], there are no internationally agreed recommendations regarding the handling of incidental findings in screening that take into account medical, medicolegal and patient perspectives. It is unclear which findings have little or no clinical consequences and which are significant enough to require further evaluation. In a recent study, only 1.8% of the pulmonary findings led to additional evaluation, while 15.3% of cardiovascular findings resulted in referral for further testing [120]. A comprehensive list of examples of incidental findings that may be identified in LDCT screening for lung cancer is given in Supplementary Appendix IV.

Molecular biomarkers

Molecular biomarkers for the early detection of lung cancer are currently still limited to research trials. However, there are great expectations that they might substantially improve the selection of high-risk individuals undergoing LCS and improve specificity for indeterminate lung nodules [37]. The clinical utility of a biomarker to identify patients' eligibility for LCS is its ability to reduce the rate of lung cancer deaths without increasing the risks and costs, or to maintain an equal rate of lung cancer deaths while assuring a reduction of risks and costs, or an optimum of both. Conversely, the clinical utility of a biomarker for lung nodule management is reflected either by earlier diagnosis with a comparable number of procedures, or the reduction of procedures without delaying diagnosis of lung cancer.

Two main noninvasive techniques for biomarkers have been tested: liquid biopsy from blood sampling (markers: cell-free DNA, proteomic signatures, mRNA, microRNA (miRNA), exosomes, circulating tumour cells and tumour-educated platelets) [130, 131]; and volatile exhaled breath compounds (techniques: infrared spectrometry, gas chromatography–mass spectrometry, solid-state sensors and mass spectrometry) [132].

Compared to LDCT screening trials, most biomarker studies have stemmed from clinical practice with relatively small populations and advanced stage lung cancer. Exosomes encompass cell-derived vesicles containing, among others, miRNA, mRNA or proteins. These non-coding fragments show aberrant expression in most types of cancer [133]. Proteomic characterisation can detect lung cancer and differentiate between adenocarcinoma and squamous cell carcinoma [134]. Circulating free DNA seems more suitable for determining driver gene mutations rather than for early diagnosis; likewise, circulating tumour cells are able to differentiate histology in metastatic disease [133]. "Electronic nose" techniques showed a specificity of 71%–100% and a sensitivity of 74%–86%, although mostly in advanced disease [135]. Furthermore, they still suffer from variability.

During screening, plasma-derived DNA did not predict lung cancer risk but predicted survival at the time of surgery [136]. Indeed, circulating DNA is mostly increased in higher stage neoplasms, making it a weak candidate for screening [137]. Conversely, miRNA signature classifiers (MSCs) that were retrospectively investigated in the MILD trial showed the potential for increasing LDCT specificity, with a remarkable five-fold reduction in the false-positive rate. Furthermore, MSCs could stratify lung cancer risk 2 years in advance of LDCT detectability [138]. Such risk stratification is now being prospectively tested within the bioMILD trial, with over 4000 people screened and LDCT planned for every 3 years except for participants with nodules ≥113 mm^3 or with MSCs showing increased risk [139]. A further approach to circulating miRNA (miR-Test) has been proposed, with an overall accuracy approaching 75% for stratification of lung cancer risk [140]. Interestingly, the MSC and miR-Test showed an overlap of five miRNAs (~35% of the total signature), which is a promising key characteristic of consistency for risk stratification.

At present, no liquid biopsy or breath exhalate-derived biomarkers exist that could be efficiently used and reliably implemented in a routine LDCT screening programme.

Cost-effectiveness of LCS

In 2014, the United Nations reinforced their political commitment to implement a national and global roadmap towards effective prevention and control of non-communicable chronic diseases. Their main priority is the goal of a 25% relative reduction in overall mortality from non-communicable chronic diseases, including cancer. Because most countries struggle with budget and sustainability constraints regarding their national health systems, it is crucial that the most cost-effective health interventions are prioritised, both at individual and population level [141].

Cost-effectiveness analysis (CEA), or cost-utility analysis, is a form of economic analysis that compares the relative costs and outcomes (effects) of different courses of action [142]. CEA is often used in the field of health services and is expressed in terms of a cost-effectiveness threshold or incremental cost-effectiveness ratio (ICER), where the denominator is a measurable gain in health (years of life, premature births averted, sight-years gained) and the numerator is the cost associated with the health gain, expressed in USD, GBP or EUR [143]. The most commonly used outcome measure is quality-adjusted life years (QALY) [142]. CEAs are often visualised on a plane consisting of four quadrants, the cost represented on one axis and the effectiveness on the other axis [143]. CEA results in country-specific decisions on "willingness to pay thresholds" that vary across different countries; one country's threshold cannot be extrapolated as guidance for another. A commonly cited cost–effectiveness threshold is based upon a country's *per capita* gross domestic product, which is extremely heterogeneous across EU countries (from <USD 10 000 to >USD 100 000). Tobacco cessation intervention has an ICER of less than EUR 2000 per QALY gained and is one of the most cost-effective interventions in medicine [144].

Policy decisions to implement LCS programmes are limited by the availability of population-level evidence to predict health system and public health impacts. Simulation models have been used to overcome this limitation [145]. An analysis of the NLST data estimated that the cost of LCS would be USD 81 000 per QALY gained [23], which is well below the threshold considered reasonable in the USA of USD 100 000

per QALY gained. Further CEAs performed in Canada and in a number of European countries [146, 147] indicate that LCS can be cost-effective in different healthcare systems, depending on factors such as inclusion criteria, algorithms for positive screen results, screening intervals and tobacco cessation interventions [10, 23, 145, 148, 149]. A CEA from the public payer's perspective indicates that LDCT screening in high-risk participants is associated with an ICER well below the one accepted by health institutions such as the UK National Institute for Health and Care Excellence [150]. LCS has been reported to be more effective in women than men and more effective in people with a higher risk of lung cancer than those with a lower risk [23]. A current CEA from Canada demonstrated that overly loose inclusion criteria may lead to a cost-ineffective situation [148]. The authors concluded that smoking eligibility criteria are a main factor influencing cost-effectiveness [148]. This observation, however, could not be confirmed by other authors who observed that, based on the NLST data, higher-risk patients are even more costly to screen [151]. With the main cost driver of ICER in the NLST being CT, any scenario in which the management of non-calcified nodules requires further CT scanning will impact on its ICER. Modern management protocols like Lung-RADS or those using volumetry are likely to decrease the number of repeat scans and thus the overall costs [152]. Furthermore, because non-lung cancer outcomes (i.e. tobacco-related comorbidities) have a heavy impact on cost-effectiveness of LCS, effective tobacco cessation interventions and measures to reduce coronary risk have the potential to improve cost-effectiveness of LCS even further [145].

Action plan

Pulmonologists and radiologists both have key roles in the set up of multidisciplinary task forces with experts from many other fields to promote LCS, ensure quality and provide continuing medical education, as well as optimal communication, with the participants. Pulmonologists have a crucial role in identifying people eligible for LCS, reaching out to family doctors, sharing the decision-making process and promoting tobacco cessation. They need to ensure that the eligible risk population understands the importance of LCS and is informed of its potential benefits, risks and harms. The role of radiologists in LCS is to ensure that LDCT is optimised with regard to high image quality, minimum dose and the most appropriate management of screen-detected "positive" nodules and incidental findings. Strict algorithms defining the exact workflow and procedures triggered by positive screen results and incidental findings have to be implemented, which involves thoracic oncologists, thoracic surgeons, pathologists and others. For screening to be (cost-)effective, it has to target a high-risk population that is not solely based on age and sex. Thus, risk prediction models should serve to identify participants for screening, in addition to determining the intensity and duration of LCS.

The ESR and ERS agree that Europe's health systems need to adapt to allow patients and citizens to benefit from organised pathways for early diagnosis of lung cancer, reduce the mortality rate of this lethal disease and limit detrimental effects. Now is the time to convince policymakers across the EU that this is an urgent societal and political need. However, inequalities in lung cancer diagnosis and care could become greater if screening is recommended but introduced unequally across Europe. Advocacy should be both top-down and bottom-up because the patient voice and involvement is crucial in raising awareness of the need to introduce screening at a national level and effectively progress its implementation. This process might be achieved by the set up and conduct of carefully designed and well-targeted demonstration programmes in several countries, focusing, among other points, on methodology, standardisation, tobacco cessation, education on healthy lifestyle, psychosocial effects, cost-effectiveness and the balance of benefits and harms.

Box 1 Action plan for implementation of LDCT LCS

European level

1a) Advocacy by relevant European medical societies and organisations (such as ERS, ESR and the European Alliance for Personalised Medicine) in collaboration with respective national societies, European patient organisations (such as European Lung Foundation, Association of European Cancer Leagues, Lung Cancer Europe) and other potential stakeholders at the EU level.

1b) Development of a recommendation or even a directive by the European Council asking for implementation of nationwide, population-based LDCT LCS programmes in EU countries.

2a) Formulation of minimum standards and analysis of benefits and harms for implementation of nationwide, population-based LDCT LCS in European countries by ERS, ESR, *etc*.

2b) Regular surveillance of latest evidence on LDCT LCS by core ERS–ESR team, adaptation of statement for minimum standards and/or creation of updates as needed.

3) Planning and, if feasible, set up of an umbrella European registry/analysis unit linked to national registries for quality assurance and further research.

National level

1a) Advocacy by relevant national medical societies in collaboration with national patient organisations and stakeholders at the national level (government, parliament).

1b) Raising public awareness by media and other communication channels.

1c) Approval of implementation of nationwide, population-based LDCT LCS programmes.

2a) Set up of a national expert group for the implementation of nationwide, population-based LCS, including patient representation in collaboration with responsible national administrative levels.

2b) Formulation of standard operating procedures for the implementation of nationwide, population-based LDCT LCS as well as nation-specific standards for infrastructure, pathways and

outcomes/quality assurance measures based on nation-specific healthcare systems:

- benefit–harm analysis, including overdiagnosis, psychosocial effects and cost-effectiveness
- estimation of the needs in infrastructure and human resources
- gap analysis
- estimation of the needs in resources for implementation and performance.

After national programme initiation:

2c) Regular surveillance of latest evidence on LDCT LCS (in collaboration with European core team), with updates of national recommendations for minimum standards, benefits and harms, psychosocial effects and adequate quality.

3) Planning and, where feasible, set up of a national registry/analysis unit for quality assurance and further research, preferably linked to European registry/analysis unit (if in place).

Local level

1a) Set up of a core expert group for planning, implementation and performance review of the local LDCT LCS including at least representation by pulmonology, radiology, thoracic surgery and oncology plus a patient representative.

1b) Definition and set up of local infrastructure, pathways and outcomes/quality assurance, including naming all involved, as well as responsible disciplines/people at the various steps of the pathway.

2) Planning and, if feasible, set up of a local registry/analysis unit for quality assurance and further research, preferably linked to a national registry/analysis unit (if in place).

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