

Summary of Lung Cancer Screening via Low-Dose Computed Tomography (LDCT)

This summary aims to provide an overview of the current situation regarding Low-Dose Computed Tomography (LDCT) lung cancer screening, encompassing the current state of implementation, research trials and key issues at stake. This summary is not intended to promote a uniform position on behalf of cancer leagues but instead describes the main areas of interest regarding lung cancer screening and offers some interpretation for member leagues based on the available evidence.

Key messages

- Lung Cancer is a major public health and societal problem. A very concerning socioeconomic gradient is evident in lung cancer survival. Efforts to address the burden of lung cancer can potentially mitigate substantial and persistent inequalities in health;
- Evidence from clinical trials of LDCT lung cancer screening shows promise in the reduction of lung cancer mortality;
- Yet, important pragmatic and economic questions remain to be answered about the potential for lung cancer screening to be implemented at scale in a real-world setting;
- Demonstration studies are ongoing in Europe. Health systems should consider investing in such focused implementation research to address the outstanding questions facing the potential future implementation of lung cancer screening;
- Decision-makers are likely to await further reliable and validated evidence generated by the pragmatic demonstration studies before deciding on further implementation;
- Screening for lung cancer may prove to be important in improving lung cancer control, however, early detection alone is not sufficient to reduce the burden of lung cancer. Countries must continue to prioritise and invest in primary prevention, including establishing tobacco-free generations, in parallel with the support needed for effective forms of early detection.

Contents

Background.....	3
Lung Cancer Screening Trials	3
Global status on the implementation of lung cancer screening.....	5
Key issues to consider for lung cancer screening programme design and future implementation	6
• Balance of benefit vs harm of LDCT screening for lung cancer	7
○ False positives.....	8
○ Overdiagnosis.....	8
○ Radiation exposure	8
• Cost-effectiveness.....	9
• Target population for screening.....	10
• Invitation strategies and informed decision-making.....	10
• Tobacco cessation	11
• Screening interval.....	12
• Nodule assessment management	13
• Testing capacity and dedicated health workforce.....	13
• Incidental findings.....	14
• Potential biomarkers	14
Future directions.....	15
Conclusions.....	16
References.....	17

Background

Lung cancer is the most frequent cancer in men and the third most common cancer in women worldwide with an estimated 2.2 million new lung cancer cases and 1.8 million deaths (both sexes) in 2020 (1). In Europe, Lung cancer is estimated to be responsible for 1 in 5 of all cancer deaths and account for 1 in 8 new cancer cases in 2018 (2). Approximately 75% of lung cancer patients will have advanced disease (stage III/IV) at the time of diagnosis (3). Despite significant progress being made in the clinical management of lung cancer in recent times, survival remains poor (4). Over 80% of lung cancer patients will survive for at least a year if diagnosed at the earliest stage compared to 15% for those diagnosed at the most advanced stage of disease (5). The poor prognosis follows a clear geographical gradient within countries and between eastern and western Europe, demonstrating sizable inequalities in the lung cancer burden (6,7).

The main risk factor for lung cancer is tobacco smoking, accounting for more than 80% of lung cancer cases (8). Tobacco use is the leading global cause of preventable illness and death and the main modifiable risk factor for cancer overall (9). Tobacco use represents an important public health issue worldwide, but particularly in the WHO European Region, where the highest levels of tobacco-use prevalence have been reported. Regional estimates suggest that around 29% of people over the age of 15 years use tobacco products, with prevalence being higher among men than women (10).

One review has shown the mortality rate among cigarette smokers is two to three times that of similar people who have never smoked, with an average reduction in life expectancy of 10 years (11). Systematic reviews have reported that lung cancer risk continues to decline as time since smoking cessation increases, but remains higher in former smokers than in persons who never smoked (12–14). Nevertheless, reducing smoking rates would have a substantial effect on the burden of lung cancer and other non-communicable diseases caused by tobacco smoking (15).

Lung cancer has a number of elements which indicate that screening may be effective and worthwhile: lung cancer has high morbidity, mortality and prevalence in many countries; the risk factors are well known and understood; and evidence shows therapeutic interventions are more effective at the early stage of the disease (15). Moreover, a potentially suitable diagnostic techniques have been identified, namely Low-Dose Computed Tomography (LDCT). In light of these factors lung cancer screening (LCS) has been explored through several large clinical trials in the USA and Europe.

Lung Cancer Screening Trials

Initial research efforts focused on investigating whether chest radiography was effective in reducing lung cancer mortality, but no significant effect on mortality reduction was found (16). Beginning in the early 2000s, subsequent research began to examine the cost-effectiveness and efficacy of lung cancer screening using Low-Dose Computed Tomography (LDCT) (17).

The largest of these trials was the **National Lung Cancer Screening Trial (NLST)** which included 53,454 participants at high-risk of lung cancer. Participants were offered either LDCT or chest radiography. The NLST reported that LDCT screening for 3 years was associated with a 20% reduction in lung cancer mortality among high-risk smokers or recent former smokers (18). There was a statistically significant increase in some other studied mortality outcomes and no decrease in all-cause mortality (RR 1.01).

In Europe, many lung cancer screening studies are currently active or have reported their findings, including: the Multicentric Italian lung detection (MILD) trial; the Italian lung study (ITALUNG); Detection and screening of early lung cancer with novel imaging technology (DANTE); the Danish lung cancer screening trial (DLCST); the Dutch-Belgian lung cancer screening trial (NELSON); the German lung cancer screening intervention trial (LUSI); and the UK lung cancer screening (UKLS) study (19).

The largest of the studies is the **NELSON trial**. It is the only randomised lung cancer screening trial in Europe sufficiently powered to determine whether low-dose CT screening reduces lung cancer mortality(20). Beginning in 2004, the NELSON study ran in the Netherlands and Belgium recruiting 15,792 participants. Those in the randomised arm of the trial underwent low-dose CT at enrolment and after 1 year, 2 years and finally 2.5 years, whereas no screening was offered to those participants in the control arm (20). The final findings of the NELSON study showed an overall 24% reduction in lung cancer mortality over a 10-year follow-up with annual LDCT screening, which increased up to 33% in women (21). However, women were underrepresented in this trial as the protocol had been initially focused on men only. Due to the interest of some women to participate, both sexes were included ultimately in the study: in total 13,195 men (primary analysis) and 2594 women (subgroup analysis).

A systematic review of 10 randomized controlled trials (RCT) reported a lung cancer mortality reduction of 12% in the LDCT group as compared to the control (no screen or chest x-ray) (risk ratio (RR) = 0.88; 95% confidence interval (CI): 0.79–0.97). For overall mortality, the review reported that no statistically significant difference was evident between the screening and control groups (22). Figure 1 displays some of the key characteristics of the major studies.

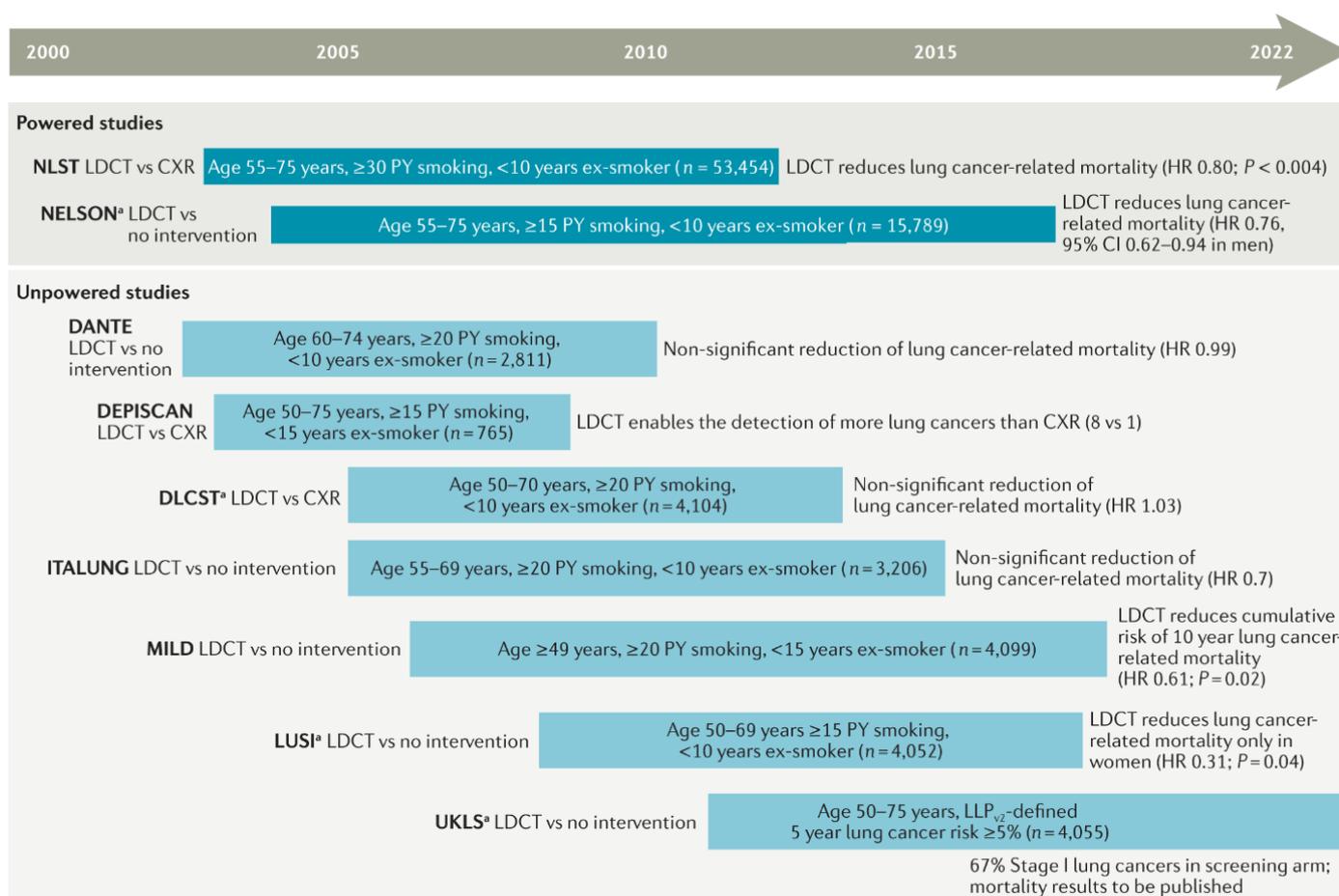


Figure 1: timeline of randomized-controlled trials (RCTs) of low-dose computer tomography (LDCT)-based lung cancer screening, showing the time from the recruitment date to the end of follow-up and relevant findings associated with each trial. NB. Screening rounds are not shown but range from 2 to 7. Abbreviations: CXR = chest radiography; PY = pack years. ^a = RCTs performing CT volumetry.¹

Global status on the implementation of lung cancer screening

Following the results of the NLST and a comprehensive review of the literature on lung cancer screening by the Agency for Healthcare Research and Quality (AHRQ), the **US Preventive Services Task Force (USPSTF)** recommends, since 2013, annual LDCT screening for people aged 50–80 years with a 20-pack-year smoking history, who are current smokers or have quit within the past 15 years (23). Yet, despite lung cancer screening being offered in almost 2,000 facilities in the USA, fewer than 2% of the eligible population received lung cancer screening in 2016 (23).

In **Canada**, the Task Force on Preventive Health Care issued its guidelines on LDCT screening in 2016 (24). The task force recommends LDCT screening for people aged 55–74 who meet the smoking history criteria laid out by the NLST (30 pack-year smoking history, who currently smoke or quit less than 15 years ago). The recommendation is graded as weak, resulting from low quality evidence, which implies that clinical practitioners should aide people considering LDCT screening in

¹ **Source:** Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction — evidence, pitfalls and future perspectives. *Nat Rev Clin Oncol.* 2021 Mar 12;18(3):135–51

making an informed decision. As of 2018, Canada does not have any organised screening programmes, although, some provinces and territories have begun planning or creating pilot studies.

In many **European countries** national authorities are assessing the pragmatic implications of the findings from the NELSON study by supporting a series of implementation research trials of LDCT screening for lung cancer (25) (26). Demonstration studies have taken place or are ongoing in several European countries including France (27), Poland (28) and the United Kingdom (29)(30). The UK National Screening Committee is due to review its recommendation on lung cancer screening in 2021 (31). In January 2020 the [**4-IN-THE-LUNG-RUN trial**](#) (*Towards INdividually tailored INvitations, screening INtervals and INtegrated co-morbidity reducing strategies in lung cancer screening*) began in five European countries. This study is the first multi-centred implementation trial on volume CT lung cancer screening amongst 24,000 males and females at high risk for developing lung cancer (26).

In **Asia**, the Anti-Lung Cancer Association (ALCA) in Japan first introduced LDCT screening to its members, most of whom were men aged 50 or older with at least 20 pack-years of smoking, in 1993 (32). LDCT screening was also launched in South Korea in 1999 among asymptomatic individuals aged 45 and older at Samsung Medical Centre (33). In China, as part of the national cancer screening demonstration program in 2010, LDCT screening was initiated in three regions with high lung cancer mortality. Following this, the Chinese government launched a cancer screening project for the five top cancers in selected urban areas of the country, with LDCT used for lung cancer screening (33).

Key issues to consider for lung cancer screening programme design and future implementation

The Council Recommendation of the European Union (2003) recommends that EU Member States implement quality assured organised, population-based screening for breast, colorectal and cervical cancer (34). To date, no other sites have yet met the ethical, social, organisational, and economic criteria necessary to warrant a recommendation for offering screening to the public. However, Europe's Beating Cancer Plan stated that the European Commission will support an update of the Recommendation to consider the latest evidence to potentially enlarge the recommendation to include other cancer sites (35).

For the implementation of cancer screening programmes, of critical importance is the balance between the benefit and harms involved in the delivery of the programmes. For the given population, the benefits (expressed in mortality reduction) should clearly outweigh the harms (including false positive results; overdiagnosis; psychological distress; and invasive management or follow-up procedures) and the programme should be cost-effective, affordable for the health system and use screening modalities that are acceptable to the target population. Moreover, communication to people offered screening must be appropriate and ensure that a fully informed decision can be made about the screening invitation (36). Presently, healthcare systems and their resources and affordability, for instance, vary substantially between EU Member States.

Five decades of research have now provided the lung cancer community with evidence to move towards a so-called SPIRAL framework, which defines the scope of future implementation research on lung cancer screening programmes, referred to as 'Screening Planning and Implementation Rationale for Lung cancer' (SPIRAL) (37).

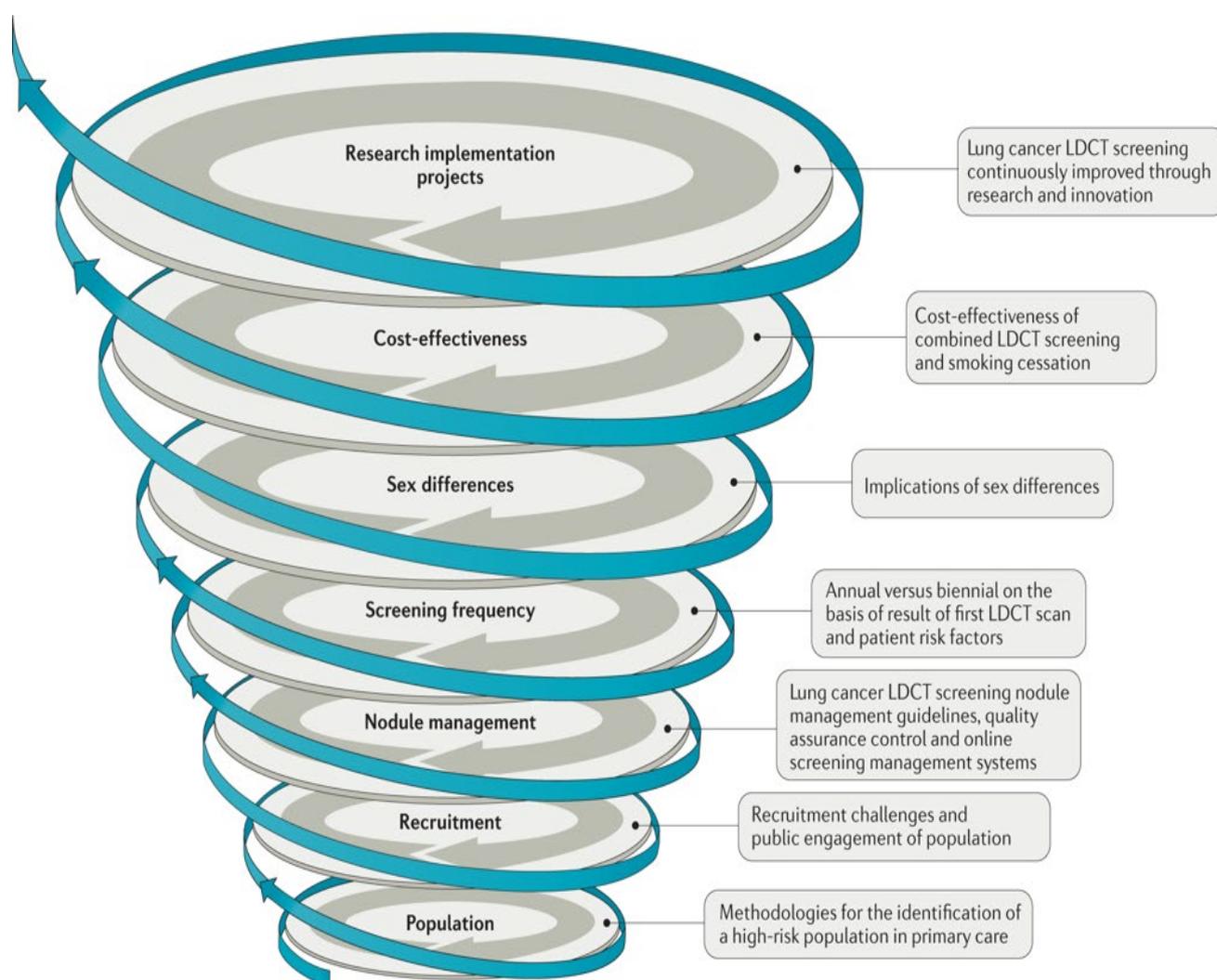


Figure 2: Framework to define the scope of future implementation research on lung cancer screening programmes, referred to as ‘Screening Planning and Implementation RAtionale for Lung cancer’ (SPIRAL). LDCT, low-dose computer tomography.²

With the SPIRAL framework in mind, hereunder are just a selection of key issues to consider when evaluating the potential future implementation of LDCT screening.

- **Balance of benefit vs harm of LDCT screening for lung cancer**

Screening causes harm through false screening results and overdiagnosis, and sometimes through harms incurred from the test itself. Screening only justified if the harm is outweighed by the benefit on a population level. The International Agency for Research on Cancer (IARC) published in April 2019 an [infographic](#) visualising the benefit and harm of lung cancer screening. Using data from the NLST interpreted using a modern protocol, it reports that if 1000 eligible people are screened 3 times annually (and followed for 6.5 years), an estimated 3 lung cancer deaths would be prevented. On the other hand, 4 lung cancer cases will be overdiagnosed. In addition, 180 people would require

² **Source:** Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction — evidence, pitfalls and future perspectives. *Nat Rev Clin Oncol.* 2021 Mar 12;18(3):135–51.

further assessment of which 13 will require an invasive procedure to rule out lung cancer (38)(39). However, this assessment was performed prior to the release of the NELSON study and, the authors have reported, is likely to underestimate the benefit of repeated LDCT screens to lung cancer specific mortality (40). A recent **EUnetHTA** collaborative assessment on lung cancer screening in risk groups drew similar conclusions (41). Also incidental findings may modify the benefits and harms, and there is little good evidence available on the trial protocols and their consequences in this respect in the trial reports and current meta-analyses (42).

- **False positives**

A key challenge is how to adequately manage the large number of relatively small nodules identified by LDCT. Approximately 20% of the screened population will have suspicious nodules in the lungs and approximately 80% of these are benign lesions (18). False-positive results are a serious concern because of the potential for subsequent unnecessary work-up procedures, which have associated risks of complications, negative impact on quality of life, and increased costs (17). During the NLST, 23.3% of all LDCT screens were false-positives, with 2.7% of participants with a false-positive screening test result facing complications after diagnostic work-up (43). A lower false positive rate (1.2%) was reported in the NELSON trial compared to the NLST as a volumetric measurement standard was used for nodule management, although at the expense of an additional category of 'indeterminate' result added as a possible outcome of the screening, which in its turn led 9.2% of the screened participants to undergo at least one additional CT scan (20)

- **Overdiagnosis**

Overdiagnosis in cancer screening is the detection of cancers that would not ever have become clinically apparent if the person had not been screened. Diagnosis of cancer causes anxiety, and treatment often causes physical harm.. There are two major contributors to overdiagnosis: indolent cancers and competing causes of death (44).

The initial estimate of overdiagnosis in the National Lung Screening Trial (NLST) with a mean of 4.5 years follow-up from the last screen, reported that 18.5% of screen-detected cancers were overdiagnosed (45). However, with longer follow-up of approximately 9 years after the last screen, this proportion fell to only 3% (46). Results from the NELSON trial were similar, estimating 19.7% overdiagnosis at 4.5 years after the final screening round, and 8.9% at 5.5 years. The findings from a systematic review reported that Among studies with follow-up periods of at least four years after the last screening visit, the risk that a lung cancer diagnosis was an overdiagnosis ranged between 18.5% in the NLST and 69.1% in the DLCST study (22).

Moreover, five microsimulation models calibrated to data sources including the NLST, indicated that fewer than 10% of lung cancers detected by screening would be overdiagnosed (47), which would place LDCT in a similar range to mammography screening. At the time of writing, there is not yet a consensus on the likely proportion of overdiagnosed cases in LDCT, thus, further studies are required (17).

- **Radiation exposure**

Considering the large number of potential participants eligible for lung cancer screening, radiation exposure from CT scanning must be carefully assessed, monitored, and evaluated. If annual screening were implemented, a person may receive up to 25 CT examinations meaning that radiation exposure is a key harm of LDCT lung cancer screening (17).

Given the radiation risk from CT, it is important to balance the benefit of early cancer detection with the potential risk of screening-induced malignancy. The common effective dose for LDCT is estimated to be 1.5 mSv (millisievert). This is roughly 4 times the exposure in mammography but lower than the 8-mSv average dose of a conventional diagnostic chest CT (48). During the NLST, people screened received an estimated 8 mSv during a 3-period, which is one radiation-induced cancer death per 2500 individuals screened in a 10–20-year period (49).

In the near term, it is anticipated that performing ultra-low dose CT scanning in lung screening, approximately 10% of the radiation dose of current LDCT, will be feasible (14). The role of ultra-low dose CT scanning is an area that may warrant further investigation (50).

- **Cost-effectiveness**

Any innovative health-care technology — either with a curative or preventative intent — requires appraisal of its added value from health regulators. Several cost-effectiveness studies on lung cancer screening have been performed using datasets from various specific clinical studies as an input, while accounting for different scenarios (37).

When examining cost-effectiveness, the NLST reported that the corresponding incremental cost-effectiveness ratios (ICERs) were \$52,000 per life-year gained and \$81,000 per QALY gained, which falls below the threshold level (\$100,000) considered to be of reasonable value in the United States (51). Microsimulations in Canada (based on NLST data) indicated that LDCT lung screening with stringent smoking eligibility criteria can be cost-effective in a population-based setting (52). Similar results were found in Switzerland (53) and in Germany where a recent study reported that lung cancer screening for a high-risk population may be more effective, but also more costly, than standard clinical care in the perspective of the payer in the German system (54).

A 2018 systematic review from the United Kingdom found that screening for lung cancer is unlikely to be cost-effective at a threshold of £20,000/quality-adjusted life-year (QALY) but may be cost-effective at a threshold of £30,000/QALY. A single screening round could be considered cost-effective. This analysis assumed no additional cost to identify the target population and recognises the barriers to participation faced by the high-risk population, which may impact upon the overall effectiveness of a programme (55). Updated clinical and cost-effectiveness evaluation is being undertaken in 2021/22 to inform the review of lung cancer screening by the UK National Screening Committee.

The latest publication of results from the NELSON trial warrants new cost-effectiveness analyses to assess the financial implications of volumetric-based lung screening, although at the time of writing they remain unpublished. A microsimulation model with a Dutch cohort of heavy smokers was conducted at a cost-effectiveness threshold of 60,000€ per life year gained (LYG). It identified the optimal screening scenario at annual screening from 55 to 80 years for men and biennial screening from 50 to 80 years for women, with an ICER of 27,600€ and 21,100€ per LYG compared with no screening, respectively, and an associated 15.9% (men) and 10.6% (women) mortality reduction from lung cancer (56).

Ultimately, the cost-effectiveness in practice (outside of trial conditions) will depend upon the implementation characteristics, which are influenced by factors including the effect of false-positive screening results, expertise of screening centres and the infrastructure of screening programmes (57).

- **Target population for screening**

Lung cancer screening differs from the other currently recommended programmes in that it specifically targets people at high-risk. There are two predominant strategies to identify the high-risk population: approaches based on age and smoking history; and risk prediction models that calculate individual risk.

Several risk predictions models have been developed to estimate the lung cancer risk of individuals incorporating sociodemographic, smoking, and clinical risk factors associated with lung cancer, including age, smoking history, sex, race/ethnicity, personal and family history of cancer, and history of emphysema and chronic obstructive pulmonary disease (COPD), among others (58).

So far only two of such models (the Liverpool Lung Project [LLPv2](59) and Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial [PLCO](60) models) have been used to identify people for screening in a clinical trial. The UKLS trial used the LLPv2 risk model to include participants with at least 5% risk of developing lung cancer in the next five years. This resulted in an almost two times higher lung cancer detection rate (2.1%) compared with the lung cancer detection rate of other European trials (19). Thus, the *European Position Statement on Lung Cancer Screening*, published in 2017, recommends that LDCT lung cancer screening programmes should use a validated risk stratification approach in the future so that only individuals deemed to be at high enough risk are screened (61). Currently, the NHS Targeted Lung Health Checks (TLHC) programme uses both LLP and PLCO, with participants being offered LDCT if they meet threshold in one or both models (62). Additionally, the Yorkshire Lung Screening Trial (YLST) aims to compare the performance of PLCO, LLP and USPSTF eligibility criteria for screening population selection (63).

A serious challenge for lung cancer screening lies in the fact that lung cancer prevalence is higher in communities with lower socio-economic status (SES), which typically have an over-representation of long-term smokers (55). Such groups often demonstrate lower uptake of other organised, population-based cancer screening programmes (64). Moreover, a recent review found that those with a lower social-economic status and women are less likely to be screened for lung cancer, even if they are at high risk (65). Attention should be paid to the underlying barriers and facilitators related to participating, especially since these populations are expected to benefit most from a population screening programme (37).

Finally, the future implementation of organised LDCT screening would most likely rely on access to adequate data that would demonstrate, at the very least, current smokers. Whilst important to the identification of the target population, detailed smoking history may be somewhat difficult to ascertain in some countries considering the context of the heterogeneous health systems in Europe. Whilst this information can be gathered at subsequent points in the screening pathway, for long-term implementation, routine collection of smoking history data may need to be optimised across Europe.

- **Invitation strategies and informed decision-making**

A corollary of the high proportion of lung cases residing in communities with low SES is the need to develop tailored, community-based approaches to reach this target population. Recent demonstration projects in the north of England have shown promising results through adopting community-based 'lung health check' approaches (29)(30). These programmes were designed to minimise barriers to participation of high-risk individuals by, for example, making the lung health check (which including a lung cancer risk assessment) available in everyday settings, such as local shopping

centres, and in some locations allowing immediate access to CT. Such examples could be used to help design community-based approaches for demonstration projects in other countries, respecting the cultural and organisational context of the respective communities.

In addition, facilitating informed decision-making of individuals offered screening for lung cancer is a prerequisite. The UPSTF recommends that lung cancer screening should not be initiated without informed and shared decision-making involving a complete discussion about the benefits and harms (66). Such approaches are necessary as they can help deliver a patient-centred care model of care and facilitate a discussion regarding tobacco cessation, for instance.

An overview of recent studies of lung cancer screening have reported weak implementation of informed decision-making in the United States (67). There has been research in the UK into informed decision making as part of the LSUT. It examined whether presenting information on benefits and harms as part of a film rather than a booklet impact on informed decision making (68).

Further research is required to design and test appropriate tools to facilitate informed decisions about lung cancer screening. A commitment to facilitating informed decision-making requires appropriate training of physicians, the provision of suitable evidence-based tools such as decision aids, and time and personnel resources, which will need to be taken into account regarding the consideration and planning toward possible future implementation (41).

Finally, a quite specific issue in applying a tailored approach is how to deal with low-risk former smokers and never smokers for which the harms of screening and follow-up may outweigh the benefits, but who experience distress or anxiety for developing lung cancer. Questions remain on how such individuals can be informed adequately to prevent screening of the low-risk population. On the other hand, lung cancer can still develop in those with lung cancer risks deemed to be too low to be eligible for participating in population screening programmes.

- **Tobacco cessation**

It is an ethical requirement that any form of lung cancer screening must offer tobacco cessation advice and follow evidence-based guidance when offering support for current smokers in their decision to quit. To date, evidence is still emerging regarding the impact of integrating tobacco cessation and LDCT screening for lung cancer (69). While it is evident that smoking cessation should be incorporated in lung cancer screening, further research is required to ascertain the optimal treatment type, modality, timing, and content of communication including the incorporation of CT results to motivate health behaviour change (70). Beginning in 2020, the Yorkshire Enhanced Stop Smoking study will measure the effectiveness of a smoking cessation service integrated within the Yorkshire Lung Screening Trial (YLST), incorporating incidental findings detected on the low-dose CT scan performed in the context of the YLST (71).

As with other types of screening, screening for lung cancer can provide an opportunity window for health promotion acting as a teachable moment (72). A review of the clinical trials indicated that whilst the process of LDCT lung cancer screening itself does not directly affect smoking behaviour, receiving positive or indeterminate results during screening has been shown to be associated with greater abstinence (73). This suggests that the communication of results from LDCT screening should be tailored to highlight the key importance of tobacco cessation.

A concern with LDCT lung cancer screening is the theoretical incentive to continue or return to smoking tobacco of screened people after receiving a negative result. Efforts should be taken to ensure that participants in LDCT screening do not receive false reassurances regarding the lifestyle risk factors and that risk compensation behaviour is not tacitly encouraged via the communication of a negative screening result (17).

Additionally, people who currently smoke whom are deemed ineligible for screening are nevertheless at an increased risk of cancer and other chronic diseases and could, therefore, be offered the option of alternative preventive interventions, such as tobacco cessation. The option of tobacco cessation programmes would have a favourable health impact among smokers not eligible for lung cancer screening, while enhancing the impact of a screening programme, as long as offering anti-tobacco counselling to subjects enrolled in screening improves the cost-effectiveness of the intervention (74). This is likely as smoking cessation interventions are highly cost-effective.

Overall, the central public health message is clear that screening is not an alternative nor competitor to tobacco cessation and this message should be unambiguously communicated in all circumstances in which LDCT lung cancer screening is concerned.

- **Screening interval**

Most trials of LDCT lung cancer screening used annual screening intervals. The exception is the NELSON study which used a progressively increasing screening interval across the screening rounds of the trial: a 1-year interval was in place between the baseline screen and second round, followed by a 2-year interval between second and third screening round, and finally a 2.5-year interval between the third and fourth screening rounds. An analysis of the 2.5-year interval of the NELSON trial indicated that this screening interval produced more interval cancers than the 1 and 2-year intervals. In addition, the proportion of lung cancers diagnosed at an advanced stage was greater than those in the shorter intervals, suggesting that 2.5-years is too lengthy an interval for LDCT lung cancer screening (19).

Annual screening has been recommended in already implemented lung cancer screening programmes based on the mortality reduction reported in the NLST for annual screening (17). Whilst evidence available is mostly concerning annual screening, results from cost-effectiveness modelling indicate that biennial (2-year interval) LDCT screening for lung cancer over 20 years might provide a similar benefit as annual screening and be more cost-effective than annual screening (74). An HTA from the UK reported that screening for lung cancer is unlikely to be cost-effective at a threshold of £20,000/quality-adjusted life-year (QALY), but may be cost-effective at a threshold of £30,000/QALY (75).

Research suggests that a risk-tailored approach, modulating screening intervals based on the results of the initial screening rounds (61), as well as additionally information from e.g., biomarkers, might also represent a cost-effective option (26), although not yet validated (76). A validated risk-stratification approach needs to be developed in order to ensure that only those people who currently smoke at high enough risk are screened, as the cost-effectiveness of screening is a function of the expected prevalence (77). Although the emergence of a validated biomarker(s) may enable the risk assessment in other populations groups beyond people who currently smoke.

- **Nodule assessment management**

A further challenge in lung cancer screening is to be able effectively manage the large number of small nodules identified in screening, many of these nodules are often benign (19). Size is an important predictor of malignancy of lung nodules; thus, it requires accurate measurement. To measure lung nodules, the largest diameter, the mean diameter, or the volume can be used (78). The European position statement on lung cancer screening identified the volumetric approach to assessing lung nodules as the most suitable method and proposed this approach for a future screening policy (61).

The data on volume is mostly taken from evidence from the NELSON trial (79), which used an approach based on nodule size and growth (80). As most nodules identified in LDCT screening are benign, the NELSON study was organised to identify fast-growing nodules, many of which still provided to be benign. Nodule growth is typically expressed in terms of Volume Doubling Time (VDT), which has been defined as the time taken for the nodule to double in volume or to increase by 26% in its diameter (81). The VDT can be used as one cut-off point for lung screening that may help to reduce the rate of false positives and overdiagnosis (82). Furthermore, retrospective data analyses show that the cut-off for negative, indeterminate, and positive screening test result could be more optimal, with more stringent cut-offs for newly detected lung nodules (26).

Moreover, a recent review of medical societies positions on lung cancer screening noted that volumetric analysis has not been established as part of the radiologic standard of care in Europe (19). This points to the wider issue of heterogeneity of guidelines from professional societies implicated in any attempt at lung cancer screening. The organisation of screening services, as well as diagnostic and treatment units, should ensure a high-quality diagnostic process and therapeutic management. The adherence to minimum technical standards; the adoption of standardised protocols and the involvement of multidisciplinary teams for the diagnostic assessment and management of screen-detected nodules; together with systematic monitoring by quality assurance boards at the national level; all represent prerequisites for the potential implementation of lung cancer screening (61). Consequently, comprehensive quality monitoring criteria are required prior to future implementation.

- **Testing capacity and dedicated health workforce**

Implementing a lung cancer screening programme requires both sufficient CT scanner capacity, trained radiologists to evaluate the screens, and health professionals to perform targeted lung health checks and lung cancer risk assessment. An additional aspect to consider is the increased demand in surgical capacity due to screening (26) and to boost smoking cessation capacity.

As mentioned, standardised protocols and essential requirements for quality are needed, alongside an adequately staffed and sufficiently trained workforce. The availability of trained staff has been identified as one of the major obstacles to overcome for lung screening. For example, the Royal College of Radiologists in the UK has reported a critical shortage of radiologists. Currently, the radiology workforce across the UK is now short-staffed by 33% and needs almost 2,000 more consultants to meet safe staffing levels and pre-coronavirus levels of demand for scans. Without more training, investment in new models of care and better retention and recruitment, by 2025 the radiologist shortfall will hit 44% (83) (84). This undoubtedly raises concerns about the radiology capacity to perform the additional screening and diagnostic exams entailed by a programme and questions about the effect on examination waiting times for symptomatic patients waiting. Estimates in England concluded that a 20% increase in workload would arise if just 3% of all current smokers received a

single LDCT scan (55). Finally, of importance for future implementation is equity of access to screening services and follow up care especially in view of the existing socio-economic gradient of lung cancer diagnosis and mortality (85).

LDCT lung cancer screening implementation will ultimately require quality of care and access to further assessment and treatment that is equivalent to or superior to that offered in the context of the research studies. Moreover, implementation will require sound and effective IT systems to support identification and call/recall of eligible population across the screening pathway.

- **Incidental findings**

Clinically relevant findings for conditions other than lung cancer can occur during LDCT screening. Incidental findings may modify the impact as to lung cancer and other diseases. More research is needed to better understand the consequences of incidental findings and impact on the benefit/harm analysis of incorporating screening for other malignancies (17). These findings can infer additional harms, both physical and psychological, that are equivalent to receiving positive screening result as well as resource use (86). Preferably, there should be systematic reviews and meta-analyses of the trials, documenting all aspects of incidental findings in the trial materials.

In a US-based study among selected Veterans Health Administration (VHA) hospitals, approximately 40% of screened patients had incidental findings such as emphysema or coronary calcifications. Although incidental findings may not require follow-up testing, they may cause patient worry and may require a clinician to counsel the patient and determine if additional testing is indicated (87). The NELSON study documented incidental findings in the screening group. Given that information on such events and their consequences is only available for the screening groups, it remains unclear whether these findings benefit or harm individuals (76).

Conversely, due to the long-term tobacco exposure, those who are eligible for lung cancer screening are also more prone to develop other major tobacco-related diseases as chronic obstructive pulmonary disease (COPD) and coronary artery diseases, which have also high incidence and mortality rates. Screening for these so-called “Big-3” tobacco related diseases is feasible within the context of CT lung cancer screening. Although the health benefits based on population-based RCTs are unknown so far, it is expected that a combined approach in the early detection and treatment of these diseases would be beneficial in this high-risk population (29).

- **Potential biomarkers**

The integration of biomarkers to the eligibility criteria for LDCT lung cancer screening has the potential to improve this situation by adding information not provided by smoking history and other factors (88). Suitable biomarkers would, thus, allow for better calibration of inclusion criteria for screening, independent of age and tobacco smoking history. Although some promising candidates have been suggested, none are currently applied in routine screening practice. Moreover, results from the Early Diagnosis of Lung Cancer Scotland (ECLS) trial and the German Lung Tumour Screening and Intervention study (LUSI) showcased the analysed biomarkers had poor sensitivity compared to current risk-prediction models. In the absence of eligible RCTs, no conclusion can be drawn about the benefit or harm of the use of biomarkers in addition to LDCT in screening for lung cancer in at-risk groups when compared to lung cancer screening using LDCT alone (76).

In addition, biomarkers may support the risk assessment and clinical management of indeterminate lung nodules (89). Most of the biomarkers tested for lung cancer screening to date screening showed varying levels of accuracy and usually often specificity (90). Research on suitable biomarkers should be embedded in future demonstration and prospective pilot trials to evaluate the contribution of identified biomarkers for defining eligibility criteria and clinical nodule management (91).

Future directions

In the future, improvement in screening selection (personalized risk-based approach) will probably result in a more favourable trade-off between harms and benefits of CT lung-cancer screening (21). While challenges remain, various trials and pilot studies are underway to evaluate the performance and feasibility of implementing **risk-based lung cancer screening in practice**. It is expected that these studies will provide answers to most remaining issues (92). It is desirable that the principles of such risk-based or risk-modified strategies to be developed for cancer screening would still satisfy also the criteria and requirements of the population-based cancer screening approaches, so that the activity would not develop to so-called opportunistic testing targeting mainly some well-to-do groups or individuals, out of the all potentially benefitting population groups.

The current **COVID-19 pandemic** has caused significant disruption in lung cancer screening programmes already in place, notably in the USA, leading to a decrease in new patients screened and an increased proportion of nodules suspicious for malignancy once screening resumed (93). Prioritising well-established population-wide cancer screening programmes for breast, colorectal and cervical cancers, while including innovative approaches for other cancer screening programmes, will be key to a resilient and sustainable recovery.

Finally, the recently published **Europe's Beating Cancer Plan (EBCP)** commits to update the Council Recommendation on cancer screening by 2022 to ensure that the recommendation reflects the latest available scientific evidence. Extending targeted cancer screening beyond breast, colorectal and cervical cancer to include additional cancers, such lung, will be considered as part of this process (35). This work will be informed by advice from the European Commission's Group of Chief Scientific Advisors, and it will consider the latest developments in cancer screening technologies, and assess advances in personalised medicine, Artificial Intelligence, big data, and other technologies, as well as operational quality assurance.

Conclusions

Lung cancer is a very serious public health challenge responsible for around 20% of cancer-related deaths worldwide. The burden of lung cancer can be reduced by decreasing exposure to known risk factors such as tobacco smoking, poor air quality and radon. Screening for lung cancer may prove to be important in improving lung cancer control, however, early detection alone is not sufficient to reduce the burden of lung cancer. Countries must continue to prioritise and invest in primary prevention, including establishing tobacco-free generations, in parallel with the support needed for effective forms of early detection.

LDCT lung cancer screening has the potential to reduce lung cancer mortality by detecting the disease at an earlier stage whereby a much more favourable prognosis is possible. Evidence arising from the clinical trials on LDCT lung cancer screening is suggestive of a protective effect on lung cancer mortality. This is welcome news but there are undoubtedly several caveats that must be carefully considered by decision-makers in the coming years.

Firstly, the clinical trials have taken place in settings where access to high-quality radiological services are available and the necessary facilities for the management of screen-detected lesions are accessible. To what extent an organised LDCT lung cancer screening programmes could achieve comparable levels of quality of service and availability of resources in practice is, as yet, not sufficiently established. However, many interesting demonstration projects are underway.

Secondly, there remain several key open issues, as elaborated in this paper, to be addressed as LDCT lung cancer screening now transitions from the experimental phase to implementation research. Chief amongst these issues is establishing the balance of benefit and harms of this method, and the cost-effectiveness, which is a requirement for decision-making about future implementation.

Thirdly, alongside the requirement for sufficient resource capacity and essential quality of service, future implementation should not come at the expense of investment in primary prevention, which must also be well resourced, and of good quality. This is particularly important given the consensus that is emerging for the need to integrate tobacco cessation with any future screening programme.

Consequently, it is timely to support implementation research of evidence generated from the clinical trials in real-world settings with carefully designed, monitored, and evaluated demonstration projects. Such projects can focus on testing the considerable open issues which remain regarding this intervention. Patient groups, medical societies and all relevant stakeholders should be consulted to carefully identify the endpoints for such projects and independent quality assurance should be ensured to evaluate the impact on the benefit and harms. Given the complexity of this issue, decision-makers are advised await the consolidated and objectively reviewed outcomes of such demonstration projects before committing further to implementing lung cancer screening. In the meantime, health systems require investment to address shortages of radiologists and improve quality of smoking status data.

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