Structured narrative review on lung cancer screening: current evidence, clinical practice implications and implementation insights from a multidisciplinary task force and patient representatives

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Lung cancer screening implementation depends on national infrastructure, available resources and national guidance. Screening services and participants would benefit from a pan-European statement harmonising the differences among countries. https://bit.ly/4muf07o

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Abstract

Introduction Lung cancer screening (LCS) is an evolving field with variations in its implementation worldwide. National LCS programmes are limited and preliminary data from national implementation are scarce.

Aim An up-to-date overview of the available literature about 12 LCS-related topics that were identified as priorities by a multidisciplinary task force (TF) panel and patient representatives as well as synthesis of published evidence to inform clinical practice and health decision-making about LCS implementation. In specific areas where the scientific evidence is limited or mixed, the limitations are discussed and best practices based on available evidence are concluded.

Materials and methods A multidisciplinary TF expert panel collaborated with patient representatives, identified 12 areas of interest and incorporated patient priorities. A systematic literature search was conducted, followed by screening, review and synthesis of available evidence.

Results There is a lack of national LCS programmes in most countries worldwide. LCS benefits and potential risks are well established. Low-dose computed tomography (LDCT) combined with smoking cessation should be offered as part of a LCS strategy to ensure optimal clinical outcomes. Age and smoking status cut-offs as well as other inclusion criteria vary and should be based on national epidemiological data. Available LCS risk predictor models and biomarkers require further clinical validation prior to implementation across the entire spectrum of LCS candidates. LCS frequency remains controversial with biennial LDCT being supported by current evidence. Technical standards, quality assurance and LCS management protocols are essential in LCS implementation.

Conclusions LCS benefits override potential risks. There is slim evidence for specific cut-off values for inclusion criteria, the optimal duration of LCS programmes and the application of LCS biomarkers in clinical practice. Smoking cessation should be integrated within LCS programmes. Ongoing scientific activity in the area is expected to provide answers in the near future.

Introduction

Lung cancer (LC) is one of the most common cancers and the leading cause of cancer-related deaths worldwide [1, 2]. Despite significant progress made in oncological treatments, radiotherapy and surgical modalities, LC survival remains low, as most LC patients are diagnosed at an advanced stage of the disease when radical treatment is not an option [3, 4].

Increasing scientific evidence has reported that low-dose computed tomography (LDCT) LC screening (LCS) diagnoses LC at an early stage in up to 70% cases and decreases LC mortality by up to 25% [5, 6]. Although there is clear benefit stemming from LCS implementation, challenges and uncertainties remain regarding how to maximise its efficiency and cost-effectiveness and minimise its harms. Optimal identification of high-risk individuals who would benefit from LCS, the management of screen-detected findings and smoking cessation interventions are only a few of the factors affecting LCS implementation and impact its efficiency, cost-effectiveness and harm minimisation [7–9]. National LCS programmes are limited and relevant preliminary data from national implementation are scarce [2]. LCS is an evolving field and there are variations in practice worldwide with regards to its implementation. This manuscript aims to form an up-to-date overview of the current evidence in LCS. In specific areas where the scientific evidence is limited or mixed, the Hellenic Thoracic Society (HTS) Lung Cancer Group task force (TF) members discuss the limitations and conclude in best practices based on available evidence.

Methods

The multidisciplinary TF was initiated by the HTS Lung Cancer Group and includes members of the HTS, the Hellenic Radiological Society, the Hellenic Society of Thoracic and Cardiovascular Surgeons and patient representatives from the Hellenic Cancer Federation (ELLOK).

The multidisciplinary expert panel included 35 respiratory physicians, six radiologists and 11 thoracic surgeons with a special interest in thoracic oncology, as well as senior trainees (early career members <40 years old) in these specialties. The panel was supported by a librarian, a registered nurse and a public health professional. 35 TF members practiced only in the national health system, nine TF members practiced only in the private health system and 11 TF members practiced simultaneously in the national health system and the private health system and were also affiliated with the Universities of Athens, Thessaloniki and Alexandroupolis. Subsequently, the expert panel represented all types of healthcare services and its members represented various geographical regions. Virtual meetings were held with a patient focus group from the ELLOK (official representative body of 40 patient organisations in Greece) to identify areas of interest and patient priorities and ensure they were incorporated into this structured narrative review's scope and narrative questions. 12 areas of interest were identified and agreed by consensus and subsequently led to 12 narrative questions based on the healthcare professionals' and patients' prioritisation. In addition to the 12 narrative questions, the TF panel specifically discussed the potential additional inclusion of further subjects in the form of separate narrative questions in this review, as follows: optimal LCS promotion, LCS recruitment and adherence strategies, LCS efficiency and cost-effectiveness, combined screening approaches of LC, and cardiovascular disease (CVD) and COPD ("big-3" diseases). The TF healthcare professionals agreed with the TF patient representatives' approach that the above should constitute a separate piece of work and therefore a consensus was reached not to include them in the current manuscript in the form of separate narrative questions as it would broaden its scope further.

The aim of this structured narrative review was to provide an up-to-date overview of the current evidence in LCS to inform best practices and guide health decision-making regarding its implementation. The scope of this structured narrative review was to identify 12 LCS related topics that were identified by the TF panel and patient representatives as priorities in clinical practice and LCS implementation. The topics included the following: current situation of LCS programmes worldwide, LCS benefits and risks, services to be included in LCS, inclusion criteria, optimal duration of LCS, optimal LCS biomarkers, optimal risk prediction models, management of LCS findings, technical standards, and quality assurance.

This review brings together available evidence on LCS implementation main issues. This may help decision-makers, health managers and multidisciplinary teams to design LCS programmes.

To the best of our knowledge, this is the only LCS review in the literature that has included priorities identified by healthcare professionals and patient representatives. It covers a more extensive timeframe of literature search (from January 2011 to March 2025) in comparison with other reviews and it presents synthesised data in narrative questions highly relevant and pertinent to patients' and healthcare professionals' priorities aiming to inform clinical practice and health decision-making about LCS implementation.

Our review presents some potential limitations. It is a structured narrative review and does not comment on the quality of evidence; rather, it syntheses published data with aim of informing clinical practice and health decision making in terms of LCS implementation.

PubMed and Cochrane databases were searched using a combination of appropriate MeSH (medical subject headings) keywords and headings, with search results from January 2011 to March 2025 and including publications in English, French and German. Additional searches were performed for documents from the ACR (American College of Radiology), ESTI (European Society of Thoracic Imaging), ESR (European Society of Radiology), NHS England and national health ministry websites worldwide, where the English versions of their websites were accessed. The full search strategy for each question, including search words and Boolean operators, is available in the appendix.

Case reports, narrative reviews, editorials, letters to the editor, commentaries, opinion reports, congress abstracts, study protocols and trials with fewer than 40 participants were excluded. In particular, the types of included studies (⩾40 participants) covered a wide methodological range and included adaptive clinical trials, multicentre studies, microsimulation studies, clinical studies, clinical trials (phases I–IV), observational studies, comparative studies, randomised controlled clinical trials, controlled clinical trials, equivalence trials, evaluation studies, validation studies and observational studies. Prisma flowcharts for each question are available in appendix 1.

Each subgroup independently screened their allocated abstracts based on the search criteria and the relevant question. Queries or disagreements were virtually discussed with the TF chairs and subsequently all abstracts were screened at a second round by them.

The multidisciplinary member subgroups performed data extraction and prepared drafts summarising the relevant scientific literature for their respective questions, which were reviewed and revised by all members prior to submission to the TF chairs. The chairs collated the subgroup outputs into a single manuscript, which was approved by all members and therefore constitutes the TF overview.

Results and discussion

Question 1: what is the current situation with national LCS programmes worldwide?

There is lack of national LCS programmes in most countries worldwide; however, LCS has been accessible in some countries through pilot studies [5, 6, 10–13]. *National LCS programmes present considerable variation in implementation, programme structure, eligibility criteria and reimbursement.*

A national LCS programme was first introduced in the USA in 2015 [14]. Guidelines for the eligibility criteria were recently updated by the US Preventive Services Task Force (USPSTF) and the Centers for Medicaid and Medicare Services by lowering the age range and pack-years (from 55–74 years old, smoking habit ⩾30 pack-years and years since quitting ⩽15 to 50–80 years old, smoking habit ⩾20 pack-years and years since quitting smoking no longer required). The main aim of these changes is expand eligibility and improve equity of screening at least, in part to address ethnic disparity [15].

Canada uses a simulation model to assess feasibility of implementing national LCS programmes in the future. Currently, there are two permanent LCS programmes in Canada for high-risk populations [16].

Brazil and Russia run implementation studies [17, 18], with the latter reported in Russian and therefore excluded due to our methodology.

In Europe, the Czech Republic launched a 5-year national LCS programme (2022–2026) [19], Slovakia has recently published guidelines for LCS implementation pending the official launch of a national programme [20], Croatia was the first European country to start a national LCS programme and issued relevant recommendations [21], and Poland recently also started a national LCS programme [22]. Switzerland has recently issued national LCS guidelines in anticipation of a future LCS programme [23] and a feasibility approach [24].

To overcome informational barriers and stigma, the UK presented LCS screening as a "lung health check", which has since been rolled out across the nationally [25], and a positive recommendation has been given for the introduction of a national LCS programme [26, 27].

There is no national LCS programme in the Netherlands; however, high-risk Dutch individuals were screened during the NELSON trial [5] and are now being screened by "4 In The Lung Run", a new European population screening study recruiting high-risk individuals from the Netherlands, Germany, UK, Spain, Italy and France [28].

Germany does not have a national LCS programme; however, the HANSE study, new holistic screening approach, is underway [29], which is anticipated to integrate several other factors in addition to the imaging evaluation of the nodules.

Italy has completed four LCS trials (DANTE, MILD, BioMILD and ITALUNG), reporting promising results regarding LC mortality benefits [13, 30–32]. There is no national LCS programme and an LCS position paper has been recently published by the Italian College of Thoracic Radiology [33].

There is no national LCS programme in Greece and the current TF's remit includes setting a framework for national implementation and national LCS guidelines.

Currently, Portugal does not have a national LCS programme. However, in December 2022, the Portuguese Minister of Health announced an expansion of the national cancer screening strategy to include lung, prostate and stomach cancers. This initiative involves pilot projects aligned with Europe's Cancer Beating Plan [34]. Furthermore, a subsequent cost-effectiveness study has provided clear evidence supporting the viability of implementing LCS in Portugal [35]. Following this development, Portugal has recently become an IARC (International Agency for Research in Cancer) Participating State. LCS has been identified as a key area of collaboration between Portugal and IARC, with particular emphasis on the evaluation of cancer control programmes [36].

Australia is planning a national LCS programme through engagement with key stakeholders that started in July 2025 [37].

Asia presents heterogeneity in national LCS programmes, with significant differences in the inclusion criteria [38–42].

Table 1 summarises all national LCS programmes available per continent including their estimated duration, funding sources and participation targets.

Question 2: what are the benefits of LCS?

The benefits of LCS have been thoroughly investigated and demonstrated over the past decade in numerous European and international studies, with LC mortality reduction being the most significant

TABLE 1 List of countries per continent with national lung cancer screening programmes, funding sources and participation targets

Country	Estimated duration	Eligibility criteria	Funding source	Frequency of screening scans	Participation targets
Europe					
Croatia	1 October 2020–2024	50–75 years old 30 pack-years <15 YSQ	Croatian Health Insurance Fund	NA	Targeted: 12 000 Screened to date: 8875
Czech Republic	1 January 2022–2026	55–74 years old 30 pack-years <15 YSQ	Czech Ministry of Health, public health insurance	NA	Targeted: NA Screened to date: 810
Poland	2020–2023	50–74 years old 20 pack-years <15 YSQ	Ministry of Health and the European Social Fund	NA	Targeted: 16 000 Screened to date: 14 000
North America					
USA	2015–NA	50–NA 20 pack-years <15 YSQ	Federal health insurance programme, the Centres for Medicare and Medicaid Services	NA	Targeted: NA Screened to date: 5.8% of high-risk population
Canada (regional)	2008–2016	50–75 years old 20 pack-years PAN-CAN model risk assessment	Third-party donations	Annual	2537/2500 participants
Asia					
Taiwan	2022–2030	45 female/50 male 74 years old (both sexes) 30 pack-years <15 YSQ	Taiwanese Ministry of Health and Welfare	NA	Targeted: 18 000 Screened to date: 3408
South Korea	2019–NA	55–74 years old 30 pack-years <15 YSQ	National Health Insurance Service	NA	Targeted: NA Screened to date: 33.1–36.6% of high-risk population
China	2012–2018	40–74 years old 20 pack-years Harvard Cancer Risk Index and seven-point risk for <20 pack-years	Public sector and University Grants, Ministry of Finance and the National Health Commission of China	Single scan	50% of high-risk population

NA: not available; PAN-CAN: Pan-Canadian Early Detection of Lung Cancer Study; YSQ: years since quitting.

[5, 6, 10–13, 32, 43] (table 2). Recent evidence suggests that LCS offers a combined screening of LC, CVD and COPD ("big-3" diseases), therefore extending its utility. In this context, implementation of national LCS programmes is considered highly important.

Reduction of LC mortality

Reduction of LC mortality is an evidence-based benefit of LDCT LCS. Two landmark prospective trials in LCS, the American National Lung Screening Trial (NLST) and the Dutch/Belgian NELSON Trial, have shown a statistically significant decrease in LC mortality of 20% and 24%, respectively [5, 6]. The NELSON trial reported profoundly decreased LC mortality for females over males (by 61% and 24%, respectively) [5] as also confirmed by the Lung Cancer Screening Intervention (LUSI) and NLST trials [6, 12]. This heterogeneity could stem from different relative counts of lung tumour subtypes occurring in males and females. Similarly, other prospective European trials [10–13, 32] and microsimulation studies [44–47] showed that LC mortality decreased by up to 39% at a 10-year duration of LCS [32]. Although, a substantial reduction in overall mortality or non-LC-related mortality has not been clearly demonstrated [10, 13], it seems that prolonged LCS has an impact on overall mortality reduction [48–50].

Early-stage LC detection

Early-stage LC detection is another pivotal evidence-based benefit of LCS. Early diagnosis is the fundamental scope of LCS and it is meant to be followed by treatment options with curative intent. Most new LC cases (up to 73%) diagnosed by LCS are early stage [5, 6, 10, 51] and amenable to treatment with curative intent (up to 87.5%) and these findings have been associated with an improved 10-year survival

TABLE 2 Benefits of low-dose computed tomography lung cancer screening

Study name, first author [ref.] (study type)	Population studied	Lung cancer mortality reduction	Early lung cancer detection	Significant life-years gained	Overall mortality reduction	Cardiovascular mortality reduction
National Lung Screening Trial **The National Lung Screening Trial Research Team** [6] **(RCT)**	55–75 years old 30 pack-years 15 YSQ	20.0% (95% CI 6.8–26.7)	50% stage IA and IB 7% stage II	Not studied	6.7% (95% CI 1.2–13.6)	Multivariate analysis showed that the three algorithm scores (Emphy-Alg, LD-Alg and CCS-Alg) were associated with CVD mortality, with odds ratios of 1.72 (p=0.003) and 2.62 (p<0.0001) for coronary calcium scores of 101–400 and above 400, respectively Similar results were shown for the incidence of CVD, with odds ratios of 1.96 (p<0.0001) and 4.94 (p<0.0001) for CCS scores of 101–400 and above 400, respectively Also, emphysema percentage demonstrated an odds ratio of 0.89 (p<0.0001)
NELSON **de Koning [5]** **(RCT)**	50–75 years old 30 pack-years <10 YSQ	24% (95% CI 0.61–0.94) in men 61% (95% CI 0.38–1.14) in women	58.6% stage IA and IB 9.3% stage II	Not studied	Not statistically significant	Not studied
MILD **Pastorino [32]** **(RCT)**	49–75 years old 20 pack-years <10 YSQ	39% (95% CI 0.39–0.95) at 10 years	39.2% stage I 5.7% stage II	Not studied	20% (95% CI 0.62–1.03) at 10 years	Not studied
UKLS **Field [54]** **(RCT)**	50–75 years old NA Risk prediction model	Not statistically significant In the meta-analysis including UKLS trial: 16% (risk ratio 0.84 (95% CI 0.76–0.92)	67% stage I 19% stage II	137.2	Not statistically significant	Not studied
ITALUNG **Bisanzi [31]** **(RCT)**	55–69 years old 20 pack-years <10 YSQ	Not statistically significant	36% stage I (p<0.001) 7% stage II	Not studied	Not statistically significant In the 2 year extended follow-up: 20% (risk ratio 0.80, 95% CI 0.66–0.96)	In the 2-year extended follow-up: 48% (risk ratio 0.52, 95% CI 0.34–0.80)
p-ELCAP **Sanchez-Salcedo [51]** **(Prospective observational cohort study)**	>40 pack-years Current or former smokers of tobacco history >20 pack-years	Not studied	73% stage I 9% stage II	Not studied	Not studied	Not studied
DEP-KP80 **Leleu [52, 82]** **(Results of second round, prospective multicentric study)**	55–74 years old ⩾30 pack-years <15 YSQ	Not applicable	4.8% carcinoma *in situ*, 64.3% stage I, 7.1% stage II,	Not applicable	Not applicable	Not applicable
USPSTF **Meza [56]** **(Modelling study)**	50–80 years old 20 pack-years <15 YSQ	Not studied	Not studied	6018–7596 estimated life-years gained per 100 000 population	Not studied	Not studied

CCS-Alg: coronary calcium score algorithm; CVD: cardiovascular disease; Emphy-Alg: algorithm on emphysema; LD-Alg: liver density algorithm; NA: not available; RCT: randomised controlled trial; YSQ: years since quitting.

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rate of 80% and 10.7 years mean survival time [51, 52]. Early LC detection is also perceived by participants as personally beneficial for early LC detection [53].

Significant estimated life-years gained and significantly decreased cardiovascular mortality
LCS has been also shown to result in significant estimated life-years gained ranging from 6018 to 7596 per 100 000 population [45, 54–56].

The LDCT protocol applied during LCS can also screen for CVD. LCS is related to significantly decreased CVD-related mortality, when assessing and reporting a known cardiovascular risk factor such as coronary artery calcification (CAC) [57]. A CAC score seems to be directly associated with the cardiovascular events and in particular a cut-off >400 may predict cardiovascular events and cardiovascular-related death [58]; therefore, its inclusion in an LDCT report may result in changes in cardiovascular management [59–61] A retrospective analysis from the NLST using machine-learning algorithms showed that Coronary Calcium Score (presented as CCS-Alg), liver density (presented as LD-Alg) and emphysema (presented as Emphy-Alg) in combination with age, gender and pack-years, can be used in clinical practice as predictors in CVD incidence and mortality [62].

Smoking cessation
Smoking cessation has been identified as an additional LCS benefit. Reported quit rates at 1 year in LCS programmes range from 11.3% to 13.5%, which are at the lower end of the estimated quit rates in LCS clinical trials [63, 64]. The success rate of smoking cessation enhances the LC-specific mortality reduction achieved by LCS. Combining smoking cessation for a period of 15 years with LDCT screening, LC-specific mortality is reduced by 38% [65]. There is also a great benefit regarding overall survival of early-stage LC patients for those who quit smoking [66].

Incorporating smoking cessation intervention into LCS can result in a 73% increase in LC deaths averted and save 200 extra life-years [67, 68].

Further to the above, current literature does not provide detailed evidence on the additional health benefits of smoking cessation in the context of LCS. There is a lack of evidence regarding the additional long-term benefit of smoking cessation in emphysema and CAC in the context of LCS programmes. However, there are several published studies on smoking cessation and abstinence rates achieved in LCS studies when smoking cessation is simultaneously offered [69–74].

However, smoking cessation is beneficial for other health entities, including emphysema and CAC, which can be incidentally detected during LCS. This alludes to the overall health benefits to be achieved through the inclusion of smoking cessation in LCS programmes, which remains to be further investigated in prospective LCS cohorts.

LCS efficiency and cost-effectiveness
LCS implementation is usually run by the national healthcare services delivered through each country's health system. The implementation of LCS as a public health intervention should be informed by cost-effectiveness and efficiency studies. LCS effectiveness is facilitated by complementary screening and smoking cessation interventions rather than either of those as a standalone. Therefore, policy makers and clinicians should offer LCS and smoking cessation as complementary interventions [75, 76].

In addition, cost-effective health interventions contribute to sustainable health systems [48, 77, 78].

COPD screening
In addition to LC and CVD, the LDCT protocol used in LCS can be applied to screen for COPD. This establishes LCS as a potential screening tool for the big-3 diseases (LC, CVD and COPD). The LDCT protocol can be used to assess quantitatively pulmonary density and bronchial wall thickness for COPD and identify undiagnosed COPD participants who are at high risk for LC [79, 80].

LCS also provides an opportunity to intervene in high-risk smokers and promote tobacco cessation, as highlighted in the "Smoking cessation" section of this manuscript.

Overall, the benefits of LCS further enhance its effectiveness and beneficial role [81], as summarised in table 2.

Question 3: which are the potential LCS risks?

Potential LCS risks are generally related to radiation exposure, false-positive results, overdiagnosis and unnecessary biopsies/interventions for benign conditions, which can potentially lead to unnecessary testing complications and psychological consequences [43, 53, 83].

Radiation cancer risk

Although LDCT is associated with significantly reduced lung radiation doses, its long-term impact on the radiation cancer risk of the screened population warrants further investigation [84, 85].

The COSMOS trial is the only study estimating long-term radiation exposure following 10 annual screening rounds in high-risk individuals [66], which was 9.3 mSv for men and 13.0 mSv for women, whereas the upper limit of acceptable radiation exposure to the public and healthcare professionals is much higher (1 $mSv \cdot year^{-1}$ and 20 $mSv \cdot year^{-1}$, respectively) [86–88]. Cancer risk and radiation exposure from LCS LDCT can be considered acceptable in view of the significant mortality reduction associated with LCS [43, 86–88].

Personalised screening strategies and risk stratification models with considerations of gender, age, interval time, duration and new technologies of LDCT imaging are needed to reduce unnecessary radiation exposure.

Radiation-related LC risk

Radiation-related LC risk stemming from LCS participation is significantly less than the LC risk carried by LCS participants due to their smoking status [53, 56, 86, 89].

Females seem to be more sensitive in quantified radiation exposure due to their breast tissue; however, there are no relevant studies addressing the radiation exposure related breast cancer risk and LC risk in high-risk females undergoing LCS [56, 86].

False-positive results

Nodules are a common LCS finding that can trigger further unnecessary investigations [5, 6]. False positivity in LCS trials ranges from 0.76% to 25.9% [5, 6, 45, 56, 81, 90–95].

This notable variation is likely due to the different definitions of positive screen results and nodule management protocols. The use of risk-prediction models and comorbidities in selection criteria further amplifies the variation in false-positive rate as nodules are more frequently detected in individuals with abnormal lung parenchyma [46, 90, 91].

Radiation reduction in LCS imaging protocols may contribute to increased false-positive rates. Radiation reduction by 50% results in a 60% increase of mean false-positive rates despite the use of computer-aided detection tools [43, 96].

LC overdiagnosis and overtreatment

Overdiagnosis is a cancer detection that would not become evident nor fatal in an individual's lifetime should they not be screened. Overdiagnosis may affect the quality of life due to unnecessary aggressive treatments for a tumour that would be clinically indolent. Overdiagnosis rates in LDCT screening programmes range from 3.91% to 21.5% [45, 46, 56, 97], while in LDCT-screening trials they reached up to 25.4% after an average follow-up of 4.5–5.8 years since the last screening visit [5, 11, 53, 98–100].

Overdiagnosis rates seem to decrease with prolonged follow-up after the final screen; as in the NLST trial, where overdiagnosis decreased from 18.5% at 3.3 years to 3.1% overall at 12.3 years [101]. Overtreatment can be a direct consequence of overdiagnosis and it is a relevant potential harm of LCS. Similarly to overdiagnosis, overtreatment is an aggressive treatment of a cancer detection that would not become fatal in an individual's lifetime should they not be treated. The growing use of LDCT screening may lead to LC overdiagnosis and treatment, and it seems to have a greater impact in women than men; therefore, it is important to improve risk-based prediction models along with gender-specific strategies to minimise overdiagnosis and overtreatment [49, 102–104].

Unnecessary interventions/biopsies for benign disease

False-positive screening tests are an attributed LCS risk as they can be followed by unnecessary invasive investigations with a rate between 0.01 and 2.0% [5, 6, 12, 13, 32, 81, 90, 91, 93, 94].

HRQoL (health-related quality of life) as a risk of LCS

LCS false-positive results or significant benign incidental findings or negative scans do not affect overall HRQoL. True positive findings are associated with worse short-term and long-term HRQoL [105]. LCS findings requiring radiological follow-up do not significantly impact HRQoL in comparison with negative LCS screens [106].

Psychosocial consequences

Psychosocial consequences pose an important risk of LCS programmes [92, 105–109].

LCS participants do not present any significant difference in anxiety levels or psychological distress within the first 4 weeks of LCS [105, 108]. False-positive results increase anxiety levels or cancer distress at 1–4 weeks following baseline LDCT [92, 106, 107] and do not pose long-term psychological consequences up to 24 months after the baseline LDCT [92, 105, 107]. Analyses of the NLST screening cohort [105], the NELSON trial [110], the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [111], the UKLS trial [82, 107], as well as meta-analyses, have demonstrated that LCS is associated with negligible physical or psychological long-term impact on participants [112] and these findings were also confirmed in real-world settings [108, 112].

Question 4: which modalities/services should be included in LCS?

Current data suggest that LDCT is the imaging modality of choice for LCS due to proven mortality reduction and early-stage diagnosis. Other imaging methods have been studied for LCS (magnetic resonance imaging (MRI) and photon-counting detector CT) with insufficient evidence to support their routine use. Pulmonary nodule Lung Reporting and Data System (LungRADS) classification and reporting are similar in LDCT and ultra-low dose CT (ULDCT); however, ULDCT is superior to LDCT in differentiating the underlying infective nature of pulmonary nodules. The use of ULDCT remains to be further validated in high-risk population subject to LC screening. Concomitant access to smoking cessation and LCS reduces further LC related mortality and it should be offered as part of the LCS programmes. There is insufficient data to support the provision of spirometry as part of LCS.

Imaging modalities

LDCT

There is solid evidence that LDCT is the imaging modality of choice for LCS due to its high sensitivity for LC detection with low radiation exposure. The benefits from LDCT screening in reducing LC mortality are well-established [6, 15, 113]. LDCT screening allows for LC diagnosis in earlier stages [114, 115]. A multidisciplinary approach including thorough pre-screening evaluation, joint decision-making, centralised coordination of screening-related care, and patient size adjusted scanning protocols is critical for a safe and successful LCS programme [116]. Novel imaging CT modalities have emerged [117]; however, further evaluation is required before they are considered in clinical practice and in the health decision-making process for LCS implementation.

ULDCT

ULDCT with full iterative reconstruction for LCS has been investigated to further reduce the risks associated with radiation exposure. ULDCT's diagnostic ability is not inferior to LDCT for nodule detection while radiation exposure is one-tenth of the exposure of conventional LDCT (0.14 *versus* 1.48) and it seems there is agreement on LungRADS criteria and reporting [118]. However, limitations concerning the relationship between the subjects' constitution and the image quality exist with regards to the nodules' characterisation and the overall evidence is not sufficient yet for standard use of ULDCT in LCS [119], although ULDCT is feasible for the evaluation of the potential infectious nature of pulmonary nodules. Pulmonary nodule LungRADS classification and reporting is similar in both LDCT and ULDCT.

MRI

In the same context of reducing radiation harms, MRI has been studied as a potential radiation-free alternative to LDCT for LCS. Although the results are comparable to LDCT for solid tumours >6 mm, there is not enough evidence to support its use due to the small number of patients studied while the requirement for specialised radiologists in MRI reporting to achieve high diagnostic performance is a limitation. Therefore, MRI is not indicated for LCS [120, 121].

Smoking cessation

Incorporation of smoking cessation into LCS reduces LC mortality and it delays overall deaths *versus* screening only, across all assumptions [122–124]. A 10% quit rate results in 14% fewer LC deaths and an up to 81% increase in healthy lung-years gained compared with LCS without smoking cessation [125].

Incorporating smoking cessation intervention into LCS can increase smoking quitting rates by 13%, save 200 extra life-years and result in a 73% increase in LC deaths averted [67, 68].

There is a great diversity in the inclusion and implementation of smoking cessation across various LSC programmes [115, 126–131] as well as the prescription of. medication (nicotine replacement therapies, bupropion or varenicline) [132].

Current evidence suggests smoking cessation should be included in LCS programmes, although there is no standardised approach on its integration and implementation [133]. More data is required concerning the most cost-effective type and modality of intervention.

Among 1034 individuals undergoing LCS through the centralised programme, 605 were currently smoking and comprised the study cohort. Nearly half (49.8%) reported interest in tobacco treatment counselling and pharmacotherapy and received a personalised treatment plan. On multivariate analysis, factors significantly associated with expressing interest in treatment included African American/Black race, higher educational attainment and returning visit type. Among the 301 individuals expressing interest in tobacco treatment, 35 (11.6%) had documentation of self-reported smoking cessation in the electronic health record. Successful smoking cessation for any length of time was significantly associated with receiving at least one longitudinal tobacco cessation counselling telephone call.

Shusted *et al.* [134] described that in a centralised LCS programme combined with smoking cessation, factors such as race, education and visit type were significantly associated with willingness to stop smoking and pharmacotherapy, while longitudinal tobacco counselling telephone calls were associated with smoking cessation.

In a well-organised LCS programme combined with smoking cessation, the addition of telephone counselling could also help to improve the overall cost-effectiveness of LCS [135].

The concept of integrated care combined with medication and counselling for smoking cessation demonstrated more prolonged benefits (highest abstinence rates up to 30%) at 6 months in an LCS setting than quitline counselling with or without medication, as described in randomised clinical trial by Cinciripini *et al.* [136].

Interestingly, this trial demonstrated that integrated care was superior to other cessation methods with a nearly two-fold improvement in quitting. Equitable access to effective medications and tobacco cessation specialists offers the greatest chance to quit smoking and significantly reduce the potential of LC [136].

Ongoing trials such as the SCALE collaboration, the YESS trial and 4 In The Lung-Run will hopefully provide answers in the coming years [137–139].

Spirometry

Spirometry's role in LCS remains arbitrary. It is an important tool to diagnose airway diseases and when performed before LDCT in the context of LCS it is likely to diagnose a large number of patients with unknown airway obstruction [140].

There are no randomised studies comparing the impact of LCS LDCT with and without spirometry and the addition of spirometry in LCS LDCT is not associated with increased LC survival or other benefit. Therefore, there is currently no evidence supporting the integration of spirometry into LCS programmes and its inclusion in the health decision-making process for change of current practice in LCS implementation pending dedicated randomised studies [72, 141].

Question 5: Who should be included in LCS?

There is no evidence regarding the optimal age criteria or the optimal quantified smoking status cut-off for inclusion in LCS. The panel supports that age and smoking status should be based on national epidemiological LC data allowing LCS adaptation to each country's needs.

There is currently no evidence to support the inclusion of never-smokers, occupational or environmental factors in LCS. The inter-relation between asbestos exposure and other LC risk factors should be clarified to determine the potential benefit for exposed individuals to be included in LCS programmes.

Patients with a previous history of LC should be offered oncological follow-up as per national guidelines rather than LCS.

Optimal age criteria

One of the core elements of any successful LCS programme is the identification and accurate selection of people at high risk for LC who would benefit from their inclusion in a large-scale LCS programme [142–146]. There are no randomised controlled trial (RCT) comparative data regarding the optimal age cut-off in LCS inclusion criteria.

Age selection criteria in LCS studies and subsequent LCS guidelines have been arbitrary [5, 6, 11–13, 15, 32, 54, 57, 147–149].

However, most reviewed papers adopted age inclusion criteria as defined by major LCS studies [5, 6, 11–13, 32, 54, 57]. The lower age cut-off values in the literature were similar to these of the NLST, UKLS and NELSON study groups (50–55 years old) while the upper age limit was 75–80 years [5, 6, 54, 150, 151] with improved LC mortality. These findings are based on epidemiological data which support that the increasing age and smoking status are relevant with the development of LC.

Smoking status criteria

There is no RCT comparative data producing solid evidence regarding the optimal quantified smoking status cut-off in LCS inclusion criteria. Reviewed papers presented a wide variation of LCS participant smoking status and its quantification [152]. Most LCS studies included participants based on an arbitrary smoking cut-off value of 20–30 pack-years [5, 6, 10–13]. This cut-off value seems meaningful when combined with current smoker status or ex-smoker status within the past 15 years, as shown by a model analysis and microsimulation study comparing eligibility strategies for LCS [153, 154]. This combination could avoid more than half of the preventable LC deaths by screening approximately 20% of all current and former smokers [155, 156]. In 2021 the USPSTF modified its initial guidelines by lowering the age and number of pack-years screening eligibility [148, 157, 158]. However, while acknowledging that the cessation of cigarette smoking decreases the risk for LC, the American Society of Cancer (ASC) panel does not agree with the 15-year restriction (*i.e.* ex-smoker status within the past 15 years) set in several trials [158]. Individuals who previously smoked have a higher risk for LC compared with those who have never smoked and the ASC claims there is no substantive drop-off in that risk after 15 years since quitting. The ASC panel also has not placed a time limit for screening eligibility after smoking cessation, because the 15-year restriction is not based on or justified by evidence. However, there is no evidence in the reviewed literature that any timeframe after smoking cessation is accepted as high risk for LC and this needs to be tailored to national public health systems considering the cost of LCS implementation and national epidemiological data.

According to the reviewed articles and the International Association for the Study of Lung Cancer Screening committee report there is still no evidence for inclusion criteria in LCS of light smokers (<10 pack-years) or never-smokers as more accurate risk prediction/benefit models should be implemented [159].

Professional and environmental exposure criteria

There is an ongoing controversy whether asbestos-exposed workers should be included in large scale LDCT screening. The major weakness of papers including asbestos exposure was the lack of data on the intensity and years of exposure on both smoker and nonsmoker population, therefore hindering any clarity on the exact effect of asbestos on lung function, mortality and cancer predisposal [160]. Against this background, the ACR suggested that there is still insufficient evidence for an LDCT screening protocol for these patients [147]. However, it has been recently proposed that workers aged ⩾50 years and with a history of ⩾5 years of asbestos exposure in combination with either a smoking history ⩾10 pack-years or <15 years since quitting or other LC risk factors (asbestos-related fibrosis and chronic obstructive or interstitial lung disease) should be eligible for LCS [161–163]. Further evidence is required prior to adoption by national LCS programmes although the asbestos ban has decreased the possibility of future RCT evidence.

There is no RCT comparative data producing evidence on air pollution exposure to be included in LCS eligibility criteria. Environmental exposure in the form of second-hand smoke exposure during adulthood was included only in one study, without an add-on [164, 165].

Family history of LC

There is limited scientific data to support the inclusion of family history of LC in LCS eligibility criteria. However, family history of LC has been included in validated LC risk stratification models and its use has been proposed in the eligibility assessment in addition to age and smoking [162, 166–169].

Reported data from Taiwan's national screening programme revealed a particularly high cancer detection rate of 6.2% (8/129) in individuals with a positive family history of all types of cancers in first-degree relatives regardless of age whilst 61.76% of all screen-detected cancers were radiographically occult [170].

Question 6: which is the optimal risk prediction model in LCS?

The panel has conducted an extensive literature review of risk prediction models in LCS and there is no set standard for an optimal model. Among all of them, the PLCOm12 model is the most used and validated externally worldwide with high sensitivity and specificity.

The risk prediction models include individualised variables and improve the identification of individuals at high risk of LC despite being smoke-free for 15 years or more [171, 172]. Similarly, risk prediction models have been developed to identify high-risk individuals regardless of smoking status and they performed well in European countries [41, 173].

The PLCOm12 risk model is a validated LC risk prediction model based on data from the PLCO [174] using 11 predictors. It includes self-reported and doctor-diagnosed COPD [166, 175]. The impact of adding obstructive spirometry to the above is not known but its standalone addition without the above improves the accuracy of an LC risk prediction [176, 177].

A PLCOm12 LC 6-year risk of greater than 1.5% has been proposed as an add-on prerequisite to the LCS eligibility criteria [151, 178].

The Liverpool Lung Project (LLP) risk model, developed from the LLP case–control study, provides a single unified model for current and former smokers as well as nonsmokers. Version 2 of the LLP risk model (LLPv2) and an updated LLPv3 have been validated [162].

The Bach model is based on a person's age, sex and smoking history, but it is predictive only for individuals between the age of 50–75 years, who smoked 10–60 cigarettes·day^{-1} for 25–55 years [179].

The Spitz model expands this concept by incorporating a panel of epidemiological risk factors, similar to the LLP model [180]. Between them, the LLP risk model's simplicity makes it more applicable for use in primary care units [181].

The choice of risk prediction models for screening eligibility is extremely important. Poor model discrimination or calibration can reduce the efficiency and cost-effectiveness of screening [182].

Various risk models include different variables. The LLP/LLPv2/LLPv3 models include only one variable for smoking duration, whereas the Lung Cancer Death Risk Assessment Tool (LCDRAT) includes smoking duration, pack-years, quit-years and intensity. Most models (*e.g.* PLCO and LCDRAT) were developed using USA data, whereas the LLP/LLPv2/LLPv3 models were developed in the UK [183–185].

PLCOm12 and LLPv2 have been implemented successfully in LCS studies; however, there is lack of evidence to conclude whether either of those is the optimal risk model [186–188].

Several models have been evaluated in population cohort studies in the USA, non-USA evaluations are scarce and none include data from UK cohorts [189–191].

The PLCOm12 risk prediction model is more efficient than the USPSTF 2013 inclusion criteria as it selects significantly more individuals for screening who are later diagnosed with LCs. Moreover, it eliminates social disparities who had been undermined in several risk models [192].

The PLCOm12 model has been validated by different research teams worldwide. It is the most commonly used risk model. It has shown acceptable performance in external validation, with higher sensitivity and specificity, resulting in an increased early LC detection rate and elevated life expectancy [83, 145, 193–198].

Question 7: which is the optimal biomarker in LCS?

There is lack of evidence suggesting the optimal biomarker in LCS; however, current data support the overall use of biomarkers can potentially complement LCS [199]. *Extensive clinical validation of biomarkers is required to lead to future integration in LCS programmes and their inclusion in health decision-making processes in LCS. The panel cannot support the use of biomarkers in LCS, only in the context of a clinical trial*.

There is a vast variety of biomarkers aiming to identify high-risk populations for LCS and complement LDCT's role with a view to improve its efficiency and diagnostic accuracy and avoid further invasive testing [200, 201].

Biomarkers explored to date were derived mainly from blood, urine or condensate samples. Some of them have synchronous use of imaging, mainly LDCT.

Serum biomarkers

The best-known panel is EarlyCDT-Lung (Oncimmune's Clinical Laboratory Improvement Amendments laboratory), which is a seven-autoantibody panel extensively validated in different cohorts [202, 203]. This panel has shown good performance in classifying indeterminate pulmonary nodules with sensitivity of 40% and specificity of 90% [204].

A second test, Nodify XL2 (Biodesix), a multiprotein plasma classifier, is also available for the classification of indeterminate pulmonary nodules and it measures 11 plasma proteins. The classifier identified likely benign lung nodules with 90% negative predictive value and 26% positive predictive value (PPV) [205].

In addition, the MSC test (a plasma microRNA signature classifier) was retrospectively evaluated in samples prospectively collected from smokers within the randomised Multicenter Italian Lung Detection (MILD) trial. Combination of both MSC and LDCT resulted in a five-fold reduction of LDCT false-positive rate to 3.7%, from 19.7% for LDCT alone [201, 206, 207].

Serum metabolites derived from gas chromatography coupled with mass spectrometry have been used to distinguish individuals with early-detected LC from healthy participants of the Polish LC screening programme with 100% sensitivity and 95% specificity. This signature of serum metabolites deserves further investigation to be established [208].

The role of LC-related tumour markers (carcinoembryonic antigen (CEA), , carbohydrate antigen 125 (CA125), cytokeratin 19 fragment (CY211), neuron-specific enolase (NSE) and squamous cell carcinoma antigen (SCC)) has been studied in LCS [209].

Their sensitivity and specificity increased when paired and the optimal combination was CEA + CA125 with sensitivity and specificity of 0.755 and 0.791, respectively [210]. Although this combination of biomarkers seems promising, it requires further validation and potential considerations should be encountered about its correlation with imaging.

Small extracellular vesicles (sEV) circulating in human biofluids have been identified as a potential source of cancer biomarkers but further testing in individuals did not support their use [211, 212].

Breath biomarkers

Exhaled breath condensate (EBC) is a promising matrix in which biomarkers can be identified with noninvasive sampling and real-time analysis; however, its composition has not been thoroughly studied. Volatile organic compounds (VOCs) and nonvolatile matters are contained in exhaled aerosol particles [213].

The high negative predictive value of VOCs obtained through breath sample analysis indicates the role of EBC in reducing cases subjected to confirmatory tests following an abnormal LCS scan [214, 215].

Miniature electronic nose (e-nose) systems can identify "breath fingerprints" based on human breath and could be used to recognise LCS participants with greater than 90% of sensitivity, specificity and accuracy. One designed e-nose system is low-cost, noninvasive and, following successful validation, it may be applicable in LCS [216]. Its combination with blood serum biomarkers could be promising, however it remains to be studied.

The use of a personalised gene-based risk tool in LCS has been shown to present a useful predictive utility to risk assignment for LC and it also increases participants' engagement in LCS for both baseline screening (uptake) and subsequent positive CT scans [217, 218].

To date, published evidence does not support the use of a single biomarker as a complementary step in LCS and possibly the use of a combination of biomarkers or a panel of biomarkers may seem the next logical step in the process. To date, published evidence does not provide solid data to support the complementary use of combinations of biomarkers in LCS and this area should be further explored [199].

Table 3 provides an overview of serum and breath biomarkers studied in LCS.

Question 8: what is the appropriate LCS interval in candidates with normal baseline LDCT?

LCS intervals longer than 2 years are more cost-effective and use fewer resources. They result in a higher proportion of diagnosis in advanced disease stage compared with shorter screening intervals. Biennial and annual LCS present similar overall and LC-specific mortality, early-stage diagnosis, quality-adjusted life-years (QALYs), sensitivity and specificity. Biennial screening is more cost-effective, uses fewer resources without compromising screening benefits and presents less overdiagnosis and fewer false positives. Agaisnt this background, the panel supports the implementation of biennial LDCT with consideration of risk stratification models to shorten the interval to annual and offer an adaptive approach, should this be required.

Annual LC screening

Annual LCS shifts LC diagnosis to an earlier stage similarly to biennial LCS and this is linked with higher resection rates (annual resection rates 74% *versus* biennial 53%, p=0.0004) and similar overall mortality, LC-specific mortality, stage II–IV LCs and interval LCs [219–221]. Annual and biennial LCS have similar recall rates for invasive procedures (1.3% annual *versus* 1.1% biennial, p=0.35) and similar other performance indicators (including detection rate of early-stage LC, frequency of interval cancer, sensitivity, specificity, PPV and negative predictive value) [95, 222]. Risk stratification models could identify candidates for LCS intervals longer than 1 year; however, the ersonalised decision-making should be the mainstay of an efficient LCS programme [55, 223–226]. Annual and biennial LCS present similar QALYs over 20 years, with annual screening using more resources [226].

Biennial LC screening

Biennial LCS may save about one-third of LDCTs with similar performance indicators to annual screening [95, 219, 222]. It presents less overdiagnosis and false positivity [56], but results in fewer LC deaths avoided and fewer life-years saved than more frequent screening [55]. On balance, biennial LCS results in similar QALYs over a 20-year screening period and is more cost-effective [226].

Biennial and annual screening are associated with a similar overall and LC-specific mortality and similar detection rate of early-stage LC. Overall, biennial screening is more cost-effective; it uses fewer resources than annual screening and reduces the number of follow-up LDCTs.

TABLE 3 Serum and breath biomarkers studied in lung cancer screening

Study name/type, references	Sensitivity (%)	Specificity (%)	Number of patients	Degree of validation (%)
EarlyCDT Lung [202–204]	54.6	90.3	235	92
Nodify XL2 (Biodesix) [205]	92	48	141	Not applicable
microRNA test [206]	77.8	74.8	1115	74.9
Serum metabolites (GC-MS) [208]	100	95	Not applicable	Not applicable
MicroRNA Signature Classifier [206–208]	87	81	939	95
Tumour markers [210]				
CEA+CA125	75.5	79.1	633	Not applicable
CEA+CY211	76.1	71.8	Not applicable	Not applicable
Small extracellular vesicles [211, 212]	Not applicable	Not applicable	243	Not applicable
E-nose [216] (LDA–Fuzzy 5-NN)	95.6	91.72	235	93.59
Volatile organic compounds [214, 215]	100	92.86	428	95.74

CA125: carbohydrate antigen 125; CEA: carcinoembryonic antigen; GC-MS: gas chromatography–mass spectroscopy; LDA–Fuzzy 5-NN: linear discriminant analysis–fuzzy k-nearest neighbour, with k=5.

Longer LC screening intervals

There is scarce data regarding longer screening intervals. The NELSON study compared various screening intervals (1.0, 2.0 and 2.5 years). The 2.5-year interval reduced the effect of screening, as it was associated with a higher proportion of advanced-stage disease [220]. Triennial screening was studied in microsimulation studies and it was associated with up to 21.9% delayed diagnosis, while potentially overlooking a substantial proportion of stage I LC. It was also associated with fewer LC deaths avoided and fewer life-years saved [55, 222]. However, the BioMILD trial showed that a triennial screening interval could be acceptable in an LCS programme with combined blood microRNA testing and LDCT in a personalised setting. This remains to be further explored in a real-life LCS programme [227].

Subsolid pulmonary nodules have a different biological nature; therefore, following their reporting in a screening LDCT they need to be followed-up as per established guidelines

Overall, longer screening intervals reduce the number of LDCTs and screening rounds, while they result in an important increase in delayed diagnosis and therefore reduce the effect of screening.

An adaptive LCS approach, starting with biennial screening and switching to annual screening based on prespecified parameters, needs to be considered further as it performs well and can be realistically applied in settings with limited CT scanner capacity and personnel shortages [228].

Table 4 summarises studies comparing different LCS intervals.

Question 9: what is the optimal duration of an LCS programme?

Currently, there is no evidence consolidating a proposed optimal or maximum duration for LCS. Considering a meaningful use of public health resources, performance status and comorbidities should be considered prior to LCS to ensure the candidate is suitable for radical LC treatment. Therefore, annual clinical evaluation is advised to inform the LCS continuance. National epidemiological data with regards to life expectancy, quality of life and LC incidence may guide the decision on LCS duration on national level.

The comparison of variable follow-up LCS durations among several studies showed that prolonged LCS beyond 5 years provides solid evidence for its long-term benefit [229]. The maximum LCS duration presented in studies is 10 years, which was associated with a significant mortality reduction in comparison with a shorter LCS duration [32]. Therefore, a prolonged intervention beyond 5 years can enhance the benefit of screening [229].

The roles of comorbidities, performance status deterioration and age in LCS duration have not been thoroughly studied. The optimal age cut-off for discontinuing LCS remains unclear, although most studies have included participants aged up to 75 years old [5, 6, 10–13]. It also remains unclear whether irreversible life-debilitating comorbidities (and which ones) constitute a reason to stop LCS and if irreversible performance status deterioration is a reason to stop LCS [146, 230]. Overall, comorbidities impact the life-years gained from LCS and this should be considered by clinicians when discussing its benefits and risks with high-risk individuals [231].

There are only two LCS studies including comorbidities and neither of them report them as a reason to stop LCS [51, 232] and there are no studies presenting data on performance status and age cut-offs in association with LCS duration.

Despite the lack of evidence, current USPSTF guidelines [15, 148, 233] suggest that LCS should cease when the candidate does not meet the requirements for radical treatment. In a pragmatic clinical setting, those requirements are defined as permanent deterioration in performance status and/or significant comorbidities excluding the candidate from receiving radical treatment.

Question 10: which are the technical requirements for LCS?

LDCT is the recommended modality for LCS and the integration of radiology software is a promising contributor to the diagnosis and management of lung nodules. The panel supports the following optimal technical standards to ensure state-of-the-art LDCT protocols and LCS quality. The panel also supports central data storage with respect to General Data Protection Regulation legislation and national monitoring.

TABLE 4 Studies comparing different lung cancer (LC) screening intervals and their summarised results

First author [ref.] year	Type of study	Number of participants	Age (years)	Screening interval	Results
Pastorino [219] 2019	Randomised controlled trial	2376	49–75	Annual, biennial	Similar overall mortality and LC-specific mortality at 10 years Biennial screening saved 44% of follow-up LDCTs
Yousaf-Khan [220] 2017	Randomised controlled trial	7915	50–75	1-, 2- and 2.5-years (consecutive rounds with increasing intervals)	The proportion of stage I LC and stage 3b/4 LC was similar after 1- and 2-year screening intervals
Sverzellati [95] 2016	Randomised controlled trial	2303	50–75	Annual, biennial	After annual and biennial screening, similar detection rate of early-stage LC, frequency of interval cancer, sensitivity, specificity, PPV, NPV Biennial screening saved one-third of LDCT scans
Silva [222] 2021	Retrospective analysis	1248	55–75	Annual (simulation for biennial and triennial)	Rate of delayed diagnosis 4.5% for annual, 13.6% for biennial and 21.9% for triennial Reduction of LDCT burden up to 25.5% for biennial and 41% for triennial screening
Robbins [223] 2019	Retrospective analysis	23 328	55–74	Annual	A negative LDCT (no >4 mm nodules) is not enough to justify a longer screening interval than 1 year The LCRAT+CT model could identify candidates for longer screening intervals than 1 year
Handy [221] 2020	Retrospective analysis	3402	55–80	Annual	LC screening with annual LDCT in a community healthcare setting demonstrated LC diagnosis (2.8%), stage shift (75% NSCLC stage 1–2 or limited SCLC), intervention frequency (14.6%) and adverse event rate (10.1%) similar to the NLST
Zhang [225] 2020	Retrospective analysis	118	40–74	Annual	No justification to increase screening interval beyond 1 year based on the PLCOm2012 model, age and smoking history
González Maldonado [99] 2021	Retrospective analysis	3395	50–69	Annual	Skipping 50% of annual screenings (participants within the five lowest risk deciles by LCRAT+CT in any round or by the polynomial model baseline screening round) would have avoided 75% (95% CI 21.9–98.7) and 40% (95% CI 21.8–61.1%) false-positive screen tests and delayed 10% (95% CI 1.8–33.1%) or no 0% (95% CI 0–32.1%) diagnoses, respectively
Meza [56] 2021	Microsimulation	288#	45–80	Annual, biennial	20 annual and five biennial consensus-efficient scenarios
McMahon [55] 2014	Microsimulation	576#	(45–60)–(75–85)	Annual, biennial, triennial	Annual screening resulted in more lung cancer deaths avoided and more life-years saved, compared with less frequent screening
Goffin [226] 2016	Microsimulation	Not applicable#	55–74	Annual, biennial	Compared with annual, biennial screening used fewer resources and resulted in very similar quality-adjusted life-years (24 000 *versus* 23 000) over 20 years

CT: computed tomography; LCRAT: Lung Cancer Risk Assessment Tool; LDCT: low-dose computed tomography; NLST: National Lung Screening Trial; NSCLC: nonsmall cell lung cancer; NPV: negative predictive value; PLCOm2012: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial 2012; PPV: positive predictive value; SCLC: small cell lung cancer. #: Scenarios.

Minimum and optimal technical LCS standards

Despite the lack of published research evidence on minimum and optimal technical LCS standards of LDCT hardware/software, LDCT scanning protocols and image acquisition, the European and American radiological societies have issued recommendations addressing the above [234–239].

Our radiology expert panel considered international recommendations in conjunction with the national LDCT infrastructure and national legislation and reached a consensus on CT hardware/software technical standards for LCS as well as a consensus on LDCT scanning protocol and image acquisition, as shown in appendix 2.

Data storage and data safety standards

There is lack of published evidence on data storage and proposed data safety standards for LCS.

Question 11: what is the optimal management of LCS findings?

An efficient LCS programme requires a streamlined process including optimised radiological protocols with emphasis on LCS finding management. Worldwide, the implementation of the optimal nodule management protocol remains a subject of debate. The panel supports the use of a volume-based nodule management protocol according to local feasibility, simplicity and radiology training. To overcome unnecessary investigations and additional costs, the expert panel supports locally agreed protocols, standardised radiology reports and specialised service referrals for incidental thoracic and extra-thoracic findings. This approach is in accordance with good medical practice.

Pulmonary nodules

Published LCS trials in Europe and the US [5, 6, 10–13] provide evidence and knowledge of the effectiveness of the various LCS finding management protocols applied [6, 11, 13, 32, 54, 240, 241].

There is a variation in practice in terms of pulmonary nodule management protocols used in various LCS trials. The LungRADS classification system implemented in the LCS programme in the US serves as a quality assurance tool. In the revised LungRADS criteria, nodule volumetry is included in addition to diameter [242], while European trials showed that volumetry and volume doubling time are more accurate than diameter-based measurements. This led to a reduction in false-positive tests, a lower number of follow-up LDCTs and fewer unnecessary diagnostics [46, 241]. More importantly, volume CT screening is efficient in the detection of early-stage LCs, therefore increasing the benefits of the LCS programme. Given the evidence-based advantages of volumetry, the EU position statement (EUPS) on LCS implementation across Europe strongly recommends and encourages volume-based management protocols of screen-detected solid and subsolid nodules [241] and ESTI provides training to radiologists to consolidate their knowledge in the EUPS protocol [243]. Each management protocol provides specific guidance on the further management of pulmonary nodules with further imaging (*e.g.* positron emission tomography CT) and invasive investigations.

Other incidental thoracic and extra-thoracic findings

Other incidental thoracic and extra-thoracic findings are commonly detected in LCS programmes (supplementary appendix 3). Examples of incidental findings that may be identified in LCS are listed in the ESR/ERS statement paper [244].

The reported prevalence of incidental findings on LCS programmes is wide [245–250]. The clinical impact of these incidental findings varies. The ESR/ERS statement paper encourages categorising them into findings requiring immediate action, further investigation or are clinically insignificant [244]. Several studies have reported a wide range of clinically relevant incidental findings that were reported [245, 247, 250]. This wide variation of reported incidental findings is likely explained by the lack of standards regarding their reporting and management. Appendix 3 highlights incidental thoracic and extra-thoracic findings that may be identified in LCS.

The ESR/ERS statement paper suggests the development of locally agreed protocols for the management of incidental findings [244] and, recently, the ACR published a relevant quick reference guide [251]. LCS programmes present a great variation in the reporting of incidental findings and there are no international agreed recommendations or algorithms regarding the clinical significance or management of detected incidental findings. To address this existing gap, a multi-European collaborative group has produced a relevant statement for incidental findings at LCS aiming to strengthen their reporting and management [252]. This will impact the effectiveness and cost-effectiveness of LCS programmes. The reporting of minor or clinically insignificant incidental findings can potentially lead to unnecessary investigations [253–257]; therefore, it is important that evidence-based practice is employed. Agreed protocols and standardised reports would be of utmost importance.

Question 12: which are the optimal quality standards in LCS?

There is a lack of published research evidence identifying optimal quality standards. However, they are addressed by international expert opinion panels and committee publications where the importance of quality control and quality assurance in LCS is highlighted. The panel supports that quality control and quality assurance measures are aligned with local infrastructure and management frameworks, as detailed below, to ensure that health decision-making for LCS is appropriately informed.

Several key elements of quality assurance have been recognised to optimise the effectiveness of LCS in daily clinical practice [54, 241, 243, 244, 258, 259].

The ESR/ERS, EU and ACR statement papers on LCS strongly recommend that quality assurance should be mandatory in all steps of LCS implementation with periodic quality controls to ensure adherence to all minimum technical standards [241, 244, 260]. Training for the implementation of quality assurance processes is also considered mandatory. The LCS project by ESTI addresses the above in detail [243].

These recommendations were reviewed by the radiology expert panel, who also considered existing national infrastructure and relevant processes and therefore reached a consensus on the proposed quality control parameters in LCS (appendix 4A).

TABLE 5 12 key questions and answers in lung cancer screening (LCS) including points for clinical practice

Question	Answers
1) What is the current situation with national LCS programmes worldwide?	Lack of national LCS programmes in most countries worldwide USA, Croatia, China, South Korea, Poland and Czech Republic have launched national LCS programmes Some countries offer access through pilot studies Variation in implementation, structure, eligibility criteria and reimbursement
2) What are the benefits of LCS?	Early lung cancer detection Life-years gained Reductions in lung cancer mortality, overall mortality, cardiovascular mortality and COPD detection in undiagnosed patients
3) Which are the potential LCS risks?	Radiation exposure False-positive results Overdiagnosis Overtreatment Unnecessary biopsies/interventions and subsequent testing complications Psychological consequences
4) Which modalities/services should be included in LCS?	Imaging (LDCT)[#] Smoking cessation[#]
5) Who should be included in LCS?	Variation in data derived from trials Age inclusion criteria should be based on national epidemiological lung cancer data[#] Smoking status inclusion criteria should be based on national epidemiological data on smoking behaviour[#] Some LCS programmes include risk prediction models complementary to inclusion criteria
6) Which is the optimal risk prediction model in LCS?	PLCOm12 is the most common used and validated model (high sensitivity/specificity)
7) Which is the optimal biomarker in LCS?	Lack of evidence and extensive clinical validation is required No evidence regarding the use of combinations of panels of biomarkers
8) What is the appropriate LCS interval in candidates with normal baseline LDCT?	Biennial LDCT with consideration of risk stratification models to shorten the interval to annual, should this be required[#] (adaptive approach)
9) What is the optimal duration of a LCS programme?	Lack of evidence for optimal or maximum duration for LCS Meaningful use of public health resources requires performance status and comorbidities to be considered prior to LCS[#] Annual clinical evaluation is advised[#]
10) Which are the technical requirements for LCS?	Hardware[#] Multidetector CT $\geqslant$64 detector rows Scan duration <10 s Slice thickness $\leqslant$1.0 mm Radiation dose $CTDI_{vol}$ $\leqslant$3.0 mGy (adjustment for weight) Software[#] Volumetry semi-automatically derived software (certified) CAD MPR and MIP
11) What is the optimal management of LCS findings?	Volume-based nodule management protocol according to local feasibility and radiology training[#] Specialised service referrals for incidental thoracic and extrathoracic findings[#]
12) Which are the optimal quality standards in LCS?	Lack of published research evidence identifying optimal quality standards Quality control and quality assurance in accordance with local infrastructure and management mechanisms[#]

CAD: computer-aided detection; CT: computed tomography; $CTDI_{vol}$: computed tomography dose index volume; LDCT: low-dose computed tomography; MIP: maximum intensity projection; MPR: multiplanar reconstruction; PLCOm2012: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial 2012. [#]: indicates points for clinical practice.

The TF panel supports the establishment of dedicated national quality assurance committees/boards that will perform periodic quality controls and ensure adherence to the pre-defined national procedures and quality standards in all aspects of LCS. These boards will be multidisciplinary and their members will be defined by the national scientific societies of respiratory physicians, radiologists and thoracic surgeons.

Medical physicists and radiographers play an integral role in ensuring quality control of technical aspects related to LDCT and therefore should be in close collaboration with LCS radiologists.

The technical aspects of quality control should include radiology hardware and software, scanning protocol-image acquisition, and image quality. Dose quality standards and quality assurance actions are also required (appendix 4B–E).

Quality assurance also includes a structured radiology (LDCT) report based on a uniform template across LCS centres as recommended by the ESTI LCS project [243, 261]. An extensive list of thoracic and extra-thoracic incidental findings that may be noted in LDCT are listed in appendix 3.

External reviewing processes should be in place to ensure accuracy of reporting and radiologists' performance.

Due the lack of relevant references in the literature, the panel supports dedicated LCS training for healthcare professionals contributing to the LCS programmes. The Hellenic radiologist expert panel agreed on a minimum of 2 years post-specialty training, working experience in a CT department as well as a minimum experience of 200 chest CT scans (independent reading and reporting) per year as prerequisites for each radiologist reporting LCS LDCT scans.

Radiographers working in LCS centres should also be appropriately trained and certified by national bodies.

Adherence to training and certification processes should be ensured by national quality assurance boards.

National LCS programmes should include imaging databases and registries recording LCs and other malignancies detected within them. These registries and databases will contribute towards auditing the LCS programmes and developing research [241].

Conclusion

The societies collaborating for this comprehensive multidisciplinary LCS statement presented a comprehensive overview of all current scientific evidence relating to the 12 narrative questions and aimed to provide answers (table 5). This comprehensive structured narrative review in LCS is the end-product of a multidisciplinary approach from its conception involving respiratory physicians, radiologists and thoracic surgeons from various clinical services and geographic areas as well as patient representatives.

LCS implementation is challenging and it depends on national infrastructure and available resources. The societies collaborating in this document considered LCS services and participants would benefit from a pan-European statement due to potential differences among various countries.

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