Lung cancer screening: where do we stand?

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Shareable abstract (@ERSpublications)
Low-dose computed tomography screening combined with smoking cessation plays an important role in the early diagnosis of lung cancer and lung cancer mortality reduction https://bit.ly/3XHuStL

Cite this article as: Hardavella G, Frille A, Sreter KB, *et al*. Lung cancer screening: where do we stand? *Breathe* 2024; 20: 230190 [DOI: 10.1183/20734735.0190-2023].

Received: 19 Feb 2024
Accepted: 19 June 2024

Abstract

Lung cancer screening (LCS) programmes have emerged over recent years around the world. LCS programmes present differences in delivery, inclusion criteria and resource allocation. On a national scale, only a few LCS programmes have been fully established, but more are anticipated to follow. Evidence has shown that, in combination with a low-dose chest computed tomography scan, smoking cessation should be offered as part of a LCS programme for improved patient outcomes. Promising tools in LCS include further refined risk prediction models, the use of biomarkers, artificial intelligence and radiomics. However, these tools require further study and clinical validation is required prior to routine implementation.

Educational aim

- To provide an overview of lung cancer screening to an audience of international healthcare professionals with a general interest in respiratory medicine.

Introduction

Lung cancer (LC) is still the leading cause of cancer death worldwide with an estimated 1.8 million deaths in 2020 [1]. Despite advances in thoracic oncology, 5-year survival in LC can be as low as 15% which is attributed to 70% of new cases being diagnosed at an advanced stage of the disease where treatment with curative intent is no longer an option [2]. The overall reduction of LC incidence and late-stage LC at the time of diagnosis are high priorities for healthcare systems worldwide. Lung cancer screening (LCS) has proven to reduce LC-related mortality by at least 20%, while the all-cause mortality is reduced by 6.7% leading to a stage shift, with more LC cases (70%) diagnosed at an early stage [3, 4]. Therefore, LCS with low-dose computed tomography (LDCT) is increasingly implemented across several countries to detect early-stage LC amenable to treatment with curative intent.

With the implementation of LDCT screening for LC, there has also been an emphasis on delivery of smoking cessation services in patients actively smoking. The combination of smoking cessation counselling and LCS has been shown to improve mortality when delivered together compared with either alone [5]. Some studies have demonstrated that patients with a positive baseline screen were more likely to quit [6–8]. Regardless, there is evidence to support that quitting smoking at any point during screening or LC assessment has been associated with improved outcomes and should continue to be a priority of LCS programmes [9].

This review aims to provide a succinct overview of LCS to an international audience of healthcare professionals with a general interest in respiratory medicine. It will present information on national LCS programmes, and it will cover current guidelines, inclusion criteria, risk stratification, biomarkers, radiomics, artificial intelligence (AI) and implementation challenges.

Current national LCS programmes

To date there are seven national LCS programmes worldwide: one in North America (USA), three in Europe (Czech Republic, Poland, Croatia) and three in Asia (China, Taiwan, South Korea) [10–16]. Parts of Canada have regional LCS programmes [17, 18] and the UK has a targeted lung health check (TLHC) programme, which is implemented in some parts of the country [19]. It is of note, there is a national recommendation in the UK for LCS that will be fully deployed by 2028–2029. In the current the National Health Service England (NHSE) TLHC programme, over 1 million participants have been invited and >3000 lung cancers diagnosed [20–22]. The UK has also provided a policy review which is an important tool in the ongoing expansion and evolution of the TLHC and it can be considered by other countries organising and delivering LCS [21].

Croatia was the first country in Europe to implement a nationwide population-based LCS programme in October 2020. It includes participants between 50 and 75 years of age, with 30 pack-years smoking history and ⩽15 years since smoking cessation. The LCS intervals are annual or biennial depending on the individualised risk stratification for LC [13, 23].

The national LCS programme in the Czech Republic has a set duration of 4 years (2022–2026) and it includes high-risk individuals aged between 55 and 74 years of age with a current or past smoking history of 20 pack-years. The time limit from smoking cessation to LCS is not defined with a set interval, differing from other programmes. Smoking cessation is included in the programme with access to services offered to patients currently smoking. LCS frequency can be annual or biennial depending on imaging results [11].

In Poland, the national LCS programme started in 2020 and is currently being reassessed for further implementation, after completion of 3 years. Similar to the Croatian programme, it includes participants aged 50–74 years with a 20 pack-years smoking history and ⩽15 years since smoking cessation [12].

Most national LCS programmes in Europe rely on primary care for participant recruitment and their funding has a limited duration with the view to evaluate the first results and impact of the LCS intervention and decide on further action. The NHSE TLHC is no longer presented in a time limited way [24]. Primary care provides data to the NHSE TLHC programme and it is involved in the management of non-urgent incidental findings. Programme delivery is variable between primary or secondary care.

European countries that have decided against a national LCS programme include France and Switzerland [25–27]. The current landscape of LCS programmes and the factors (barriers and enablers) impacting adoption by individual countries are under review on a national level basis with an anticipated update after 2025 [23, 25].

The US national LCS programme commenced in 2015 with over 4000 LCS centres [10]. The eligibility criteria were updated in 2021 to include current or past-smokers aged 50–80 years with ⩽15 years since quitting smoking [10]. However, recent guidelines by the American Cancer Society (ACS) suggest LCS in all past-smokers with 20 pack-years smoking history regardless of the length of time since their smoking cessation [28].

In Asia, the longest standing national LCS programme is in China, which was implemented in 2010. Participants are eligible if they are over 50 years of age, have a current or past smoking history and have quit within the past 15 years. China is the first country worldwide to officially include participants with a history of chronic lung disease or a family history of LC. LCS frequency is annual unless otherwise specified by findings [14].

South Korea has a national LCS programme which commenced in 2019 and it is ongoing [15]. Inclusion criteria are similar to the USA in terms of age (50–80 years old) and time since smoking cessation (⩽15 years) but require a larger smoking history of over 30 pack-years [15]. It is of note that radiologists require training on use of the Lung-RADS nodule management protocol and subsequent LCS accreditation.

Taiwan is the first country running a national LCS (2022–2030) programme that includes nonsmokers with a family history of LC. The programme is based on scientific evidence and a framework generated by a multidisciplinary panel of experts [16].

Despite many similarities across programmes, no two programmes are identical (see table 1). All countries with national LCS programmes present with diverse implementation strategies and funding duration.

TABLE 1 Overview of international guidelines on lung cancer screening and their most important eligibility criteria

Continent	Guidelines	Population age (years)	Smoking history (pack-years)	Screening modality	Frequency	Other considerations
North America	USPSTF (2021) [22]	50–80	⩾20 (smoking-cessation took place <15 years ago)	LDCT	Annually	
	NCCN (2023) [23]	⩾50	⩾20	LDCT	Annually	
	ACS (2023) [16]	50–80	⩾20	LDCT	Annually	
Asia	Republic of China (2018) [9]	50–74	⩾20 (smoking-cessation took place <5 years ago)	LDCT	Annually	
	Japan (2018) [27]	>40	No criterion	CXR and sputum cytology	Annually	LDCT is not recommended as a population-based screening tool, but optional for high-risk populations
	Republic of Korea (2015) [10]	55–74	⩾30 (smoking-cessation took place <15 years ago)	LDCT	Annually	
	Taiwan (2019) [11]	50–74	⩾30 (smoking-cessation took place <15 years ago)	LDCT	Biannually	Never-smokers with family history are included in age categories: 45–74 years (women) or 50–74 years (men)

USPSTF: US Preventive Services Task Force; NCCN: National Comprehensive Cancer Network; ACS: American Cancer Society; LDCT: low-dose computed tomography; CXR: chest radiograph.

Current LCS guidelines: who should be screened for LC?

LCS guidelines serve to provide selection criteria for inclusion of a population at elevated risk for developing LC and is most likely to benefit from participating in currently available LCS programmes or pilot studies [29]. These clinical practice guidelines are based on the latest scientific data evaluating the effectiveness of LCS using LDCT [30]. However, the inclusion criteria for LDCT screening of LC are not universally implemented across all countries due to different local conditions [31]. Being country-specific, the screening recommendations therefore vary according to nationally approved guidelines. Although there is no universal consensus on the precise "high-risk" population to whom LCS should be offered, tobacco use history is a known risk factor for LC and thus, remains a key selection criterion for LCS [29].

Various guidelines on LCS have been published by professional societies and governmental organisations worldwide in the past decade. These guidelines have mostly been based on the American National Lung Screening Trial (NLST) and the Dutch–Belgian NELSON trial results, published in 2011 and 2020, respectively, demonstrating a all-cause mortality reduction with LDCT screening [3, 4]. An overview of current guidelines on LCS is presented in table 1.

The first guideline on LCS worldwide was established by the USA, in 2013, where screening eligibility was centred on age and tobacco consumption at inclusion, as well as how much time had elapsed (in years) since quitting smoking for former smokers [32]. The US Preventive Services Task Force (USPSTF) published their first recommendation supporting annual screening for LC using LDCT in high-risk populations, defined by age (55–80 years), smoking status (current smoker or having quit within the past 15 years) and a smoking history of at least 30 pack-years [32]. An updated version of the USPSTF LCS guidelines was published in 2021 based on additional data from the NLST and NELSON trials suggesting benefits of screening with more extensive criteria [4, 33, 34]. The inclusion criteria were broadened to encompass a larger proportion of the "most-at-risk" individuals, with the previous minimum age of 55 years lowered to 50 years (the maximum age of 80 years remained the same) and the cumulative smoking exposure decreased to ⩾20 pack-years from the earlier cut-off of ⩾30 pack-years. These criteria were also adopted by the National Comprehensive Cancer Network (NCCN), who have provided annual updates on LCS recommendations since 2012 [34, 35]. Similarly, in 2023, the ACS LCS guidelines from 2013 were updated to reflect the findings of a comprehensive systematic review carried out by the ACS guideline development group [28]. In the newly amended ACS 2023 LCS recommendations the age range for inclusion mirrors that of the USPSTF guidelines by including individuals aged 50–80 years (previous age range: 55–74 years), current and former smokers with at least a 20 pack-years history of cigarette smoking [28]. It is important to note that the most recent ACS 2023 LCS guidelines differ from the newest USPSTF 2021 LCS guidelines by not requiring a time interval since quitting smoking and

offering LCS to all past smokers with at least a 20 pack-years smoking history [28]. Despite minor differences in eligibility criteria, all American guidelines agree on a screening frequency of annual LDCT in high-risk populations.

In Asian countries, a higher incidence of LC is seen among never-smokers compared with European countries, warranting differing eligibility criteria than the NLST [14–16, 36, 37]. For instance, Japan does not include smoking history as an eligibility criterion. Despite the availability of LDCT, many Asian countries have yet to establish regular LCS programmes. This is primarily due to various challenges, including issues related to cost, reimbursement, accessibility, infrastructure and staffing limitations. There is also a reluctance of eligible high-risk individuals to undergo screening procedures and the absence of well-defined guidelines may limit uptake.

In Europe, to date, there are no unified guidelines on LCS provided by professional or governmental organisations. However, in November 2022, following a recommendation of the European Council regarding LCS, two European Respiratory Society task forces were formed to provide a technical standard for a high-quality LCS programme and a management protocol for incidental LCS findings [38, 39].

Subjects with other known risk factors for LC, apart from age and tobacco exposure, have not been consistently included in LCS trials and guidelines to date [40]. Consequently, there is an ongoing debate about whether it is beneficial to invite other cohorts for LCS, for instance nonsmoking individuals with a prior cancer history, genetic predisposition for malignancy, or occupational/environmental exposure [30, 41, 42]. For this reason, there has been a greater shift towards research on individualised risk assessment for LCS to integrate various risk factors into an individualised risk prediction score [43]. The use of risk-prediction model-based inclusion in LCS could help pinpoint high-risk patients who currently do not meet the current screening guidelines. Risk prediction-based screening could improve sensitivity without decreasing specificity and maximise the benefits while minimising harm from LCS [43]. More research is needed to determine the optimal screening criteria for LCS [30].

Risk stratification in LCS: where and how can it be applied?

The optimal risk stratification model to select patients for screening is one of the key issues that limits the implementation of LCS Europe wide. This is a focus in current research as screening based on individual LC risk has the potential to improve the balance between the benefits and harms of population screening.

In the two major LCS trials (NLST and NELSON), only smoking history and age were used as the inclusion criteria for enrolment [3, 4]. However, despite these two factors contributing significantly to the development of LC, they do not specifically determine the individual risk of the participant. Consequently, various prediction models have been developed to provide individualised LC risk and include more risk variables. Table 2 presents an overview of the different predication models with the corresponding predictable clinical variables.

Tammemägi *et al.* [44] developed the prostate, lung, colorectal and ovarian cancer screening model ($PLCO_{m2012}$) for 6-year LC risk. This model has been externally validated in different countries [51]. The $PLCO_{m2012}$ predicts LC risk with higher accuracy and efficiency compared with the NLST criteria with respect to sensitivity, deaths averted, screening resources and reduction of race and sex disparities [52].

The Liverpool Lung Project risk model (LLP) provides an estimated 5-year LC risk based on risk factors that are gathered through a questionnaire [53]. Validation of this model demonstrated good discrimination and evidence of predicting LC that was better than smoking history and family history alone. In general, models that include more variables for risk assessment other than only age and smoking history perform better in preventing LC death [54, 55]. In the UK, LCS includes patients aged 55–74 years with a LC risk threshold of >1.51% by the $PLCO_{m2012}$ model (6-year risk) and $\geqslant$2.5% risk of LC over 5 years for the LLP version 2 model (5-year risk) [53–55]. LLP version 2 has evolved into an updated, more accurate version 3, which is not the same as the version used in the NHSE TLHC programme. The risk model has been developed for individuals aged 50–79 years old, current, past or never-smokers. It is based on age, gender, smoking duration, family history of LC, exposure to asbestos, previous history of pneumonia and previous diagnosis of cancer. It is applicable to nonsmokers, former smokers and current smokers [56].

In 2023, a team of researchers from the University of Oxford and the University of Nottingham developed a new prediction tool, called “CanPredict”, which estimates 10-year LC risk. This tool has undergone internal and external validation using population-based data in the UK [50]. Compared to other LC

TABLE 2 Overview of the different predication models with the included predictable clinical variables

Prediction models	Included predictable variables	Cumulative risk prediction
$PLCO_{m2012}$ [3, 44]	Age Smoking status Smoking intensity Smoking duration Number of years quit for ex-smokers Education (in six levels) Ethnicity BMI Personal history of LC Family history of LC History of COPD	A 6-year risk
Liverpool Lung Project version 2 [45]	Age Smoking duration (cigarettes, pipe and cigars) Gender Previous history of respiratory disease (COPD, emphysema, bronchitis, pneumonia, tuberculosis) History of previous cancer Family history Occupational exposure to asbestos	A 5-year risk
Bach *et al.* [46]	Age Gender Exposure to asbestos Smoking duration Smoking intensity Duration of smoking abstinence	A 10-year risk
Spitz *et al.* [47]	Age Gender Exposure to asbestos Smoking status Smoking duration (pack-years) Duration of smoking abstinence History of COPD Hay fever Occupational exposure to asbestos Occupational exposure to dust Family history of cancer Family history of any smoking-related cancer	A 1-year risk
Kovalchik *et al.* [48]	Age Gender BMI Family history of LC Smoking in pack-years Duration of smoking abstinence Emphysema	A 5-year risk
LCDRAT [49]	Age Gender Ethnicity BMI Education Smoking duration Smoking intensity Duration of smoking abstinence COPD or emphysema History of previous cancer Family history of LC	A 5-year risk
CanPredict [50]	Age Gender Ethnicity Socioeconomic status Smoking status	A 1–10-year risk for different ethnicities

Continued

TABLE 2 Continued

Prediction models	Included predictable variables	Cumulative risk prediction
	Smoking intensity Alcohol BMI COPD Asthma History of previous cancer Family history of LC Exposure to asbestos Venous thromboembolism	

$PLCO_{m2012}$: prostate, lung, colorectal and ovarian cancer screening model; BMI: body mass index; LC: lung cancer.

prediction models, the CanPredict model showed the best performance in discrimination and calibration. It also showed a higher sensitivity than the $PLCO_{m2012}$ model and LLP version 2 model, but has not yet been used clinically in LCS across the UK.

Another critical point in the context of risk stratification in LCS is, among sex, the biological provenance, which is in LCS studies often described as "race" or "ethnicity". There is a body of evidence proving that there are "racial or ethnic differences" in LCS that do impact screening eligibility, and, thus, lead to health disparities [57–59].

A recent diagnostic study from the USA found that removing "race" and "ethnicity" reduced the ability of the life-years gained from screening–computed tomography (LYFS-CT) prediction model to identify high-benefit "racial" and "ethnic" minority individuals and reduced screening eligibility for African American individuals while eligibility for other groups increased. The study reported on a counterfactual eligibility model ("LYFS-CT NoRace") that was shown to increase eligibility, maintain predictive accuracy across all "racial" and "ethnic" groups, and avoid excluding individuals from screening based on "racial" and "ethnic" minority status [60]. The authors concluded that "thoughtful use of race and ethnicity data in prediction models may help reduce disparities".

In our opinion, to improve the risk stratification for LCS in the future, a Bayesian approach should be applied in screening assessment. This means that the potential risk criteria of the patient should be continuously reassessed and added information should be incorporated such as CT scan results or updated clinical features. Currently, no LCS outcomes are included in risk stratification and in most countries, the patients' medical files are not nationally available or accessible which may limit this approach to risk prediction models. Incorporating screening outcomes, such as a negative baseline CT screen, for further risk stratification has been shown to maximise the cost-effectiveness of LCS programmes [51, 61, 62].

There has equally been a movement towards simplifying risk-based screening. Many risk models include detailed histories and questionnaires which may limit their uptake or compromise the accuracy of patient-reported data. Recent studies have demonstrated that risk assessment can be simplified without compromising performance, but this model, developed at University College London, still requires further validation prior to clinical use [63].

There is continuous research into optimising LCS with several anticipated studies. It is expected that the current ongoing screening trials, including the European 4-IN-THE-LUNG-RUN [64], the SUMMIT study (ClinicalTrials.gov identifier: NCT05186753) and the International Lung Screening Trial (NCT02871856), will further improve our understanding of the remaining challenges and offer ways to refine screening programmes [65, 66].

LCS blood-based biomarkers

A useful biomarker must influence clinical decision making in a manner that leads to improved patient care. Biomarkers as noninvasive diagnostic tools are developed to assist with the early detection of LC and may be applied in the LCS setting and lung nodule evaluation [67]. Biomarkers in LCS can fulfil the following tasks [67, 68].

- They can be useful for both the early detection and diagnosis of disease, which may decrease the number of unnecessary radiological tests performed.
- They can stratify cancer risk to further enrich the screening population and augment existing risk prediction.
- They can be used to distinguish benign from malignant nodules in LCS.

The biomarker development for early detection of cancer contains five phases [69]: 1) discovery, 2) assay validation, 3) retrospective longitudinal studies, 4) clinical validation, and 5) clinical utility. Nevertheless, even after a biomarker is well validated in multiple large prospective cohorts, several further steps need to be considered before it can be feasibly deployed in the population setting. Table 3 outlines the considerations specifically related to implementations after validation and clinical utility assessment.

Candidate biomarkers for LC early detection are studied in blood (serum, plasma), urine, exhaled breath, airway epithelium, sputum, bronchoalveolar lavage fluid, and tumour [43, 67]. The most promising biomarkers currently being studied for the early detection of LC include [43, 67]:

1. autoantibodies,
2. blood proteins,
3. complement fragments,
4. microRNA,
5. circulating tumour DNA, and
6. DNA methylation.

Many studies have tested specific proteins and/or autoantibodies in the context of LCS. In these studies, diagnostic measures dispersed considerably: sensitivity 30–97%, specificity 20–96%, positive predictive value (PPV) 5–97%, and negative predictive value (NPV) 84–97% [68, 69, 71, 72]. The wide range of diagnostic accuracy in these blood-based methods shows not only the heterogeneity of study cohorts and the relatively small study populations but also the urgent need for multimodal assessment of LC risk. Pulmonary nodule assessment remains an ongoing clinical problem and there are currently studies trying to evaluate the use of

TABLE 3 Key considerations for biomarker implementation for low-dose computed tomography eligibility assessment

Challenges	Mitigation strategies
Cost-effectiveness	Quantify cost-effectiveness based on real-world biomarker panels Evaluate biomarker-informed screening pathway Assess evidence based on different healthcare settings
Generalisability	Define target population and ensure representativeness of the study population Address diverse ancestral backgrounds in the study population to minimise racial disparities
Screening behaviour and uptake	Assess the extent of the biomarker as a motivator for screening/risk reduction for the high-risk groups, and screen de-prioritisation for the low-risk groups Evaluate biomarker-related changes to the consultation process and physician acceptance Monitor early outcome and impact due to biomarkers on screening behaviours
Equity	Population-based organised screening programme integrated into the healthcare system instead of opportunistic screening Address underserved communities Account for differences due to race, biological sex, or gender social construct Evidence-based policy with clear governance
Risk communication	Accurate and clear risk communication regarding the potential benefit and harm Identify opportunities to promote risk reduction Professional training for biomarker result interpretation targeting healthcare professionals Public education related to biomarker implication
Benefit–harm balance	Centre of the implementation success Risk model-based screening strategy is associated with a better benefit–harm balance If the biomarker test can help to inform the optimal screening pathway such as time of initiation and intervals, it can potentially reduce the burden of healthcare utilisation and follow-up procedures while maintaining the benefit of mortality reduction

Adapted from [70].

biomarkers in differentiating benign from malignant nodules [68, 69]. More recently, studies have combined several biomarkers, such as a serum-based seven-autoantibody panel and serum carcinoembryonic antigen with an AI-driven CT assessment of pulmonary nodules to identify the nodules requiring interventions [71].

Table 4 gives a comprehensive overview about a current selection of blood-based biomarkers in LCS including targets, clinical purpose and critical diagnostic measures (*e.g.* sensitivity, specificity, PPV, and NPV).

Multiparametric investigation and stratification of pulmonary nodules is a new area of interest with anticipated clinical impact [72, 92]. Cancer detection in early stages has been investigated with the concurrent use of multi-cancer early detection tests with existing screening protocols or the concurrent use of cancer biomarkers and computer learning models to identify a test for early LC diagnosis [72, 92].

Translating the use of biomarkers in clinical practice in LCS remains a common theme in research. The MILD screening trial showed that the combination of a prespecified circulating microRNA (miRNA)

TABLE 4 Selected blood-based biomarkers

Biomarker	Specimen	Clinical purpose	DP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Ref.
Specific proteins and/or autoantibodies								
6 AAB: p53, NY-ESO-1, CAGE, GBU4-5, Annexin 1, SOX2	S	D	CV	37	90	8	99	[73]
EarlyCDT-Lung: 7 AAB: p53, NY-ESO-1, CAGE, GBU4-5, SOX2, HuD, MAGE A4	S	D	CV	47	90	10	99	[74]
EarlyCDT-Lung: 7 AAB: p53, NY-ESO-1, CAGE, GBU4-5, SOX2, HuD, MAGE A4; 6 AAB: p53, NY-ESO-1, CAGE, GBU4-5, Annexin I, SOX-2	S	D	CV	37	91	16	97	[75, 76]
Radiomics, CEA, 7-AAB panel: p53, GAGE7, PGP9.5, CAGE, MAGEA1, SOX2, GBU4-5	S	D	CV	82	90	97	NA	[71]
5 AABs: TTC14, BRAF, KLF8, TLK1, KRT8	P	D of IPN	CV	30	88	NA	NA	[77]
3 proteins and 1 AAB: CEA, CA-125, CYFRA 21-1, NY-ESO-1	S	D	CV	77	80	7	99	[78]
4 proteins and 1 AAB: CEA, CA-125, CYFRA 21-1, HGF, NY-ESO-1	S	D	CV	49	96	5	96	[79]
PANOPTIC trial: 2 proteins: LG3BP and C163A	P	D of IPN	CV	97	44	25	98	[80]
6 proteins: CEA, CA 15.3, SCC, CYFRA 21-1, NSE, ProGRP	S	D	CV	89	82	87	84	[81]
5 proteins: ALDOA, COIA1, FRIL, LG3BP, TSP1	P	D of IPN	CV	92	20	26	90	[82]
3 proteins: EGFR, ProSB, TIMP1	P	D of IPN	CV	94	33	32	94	[83]
ctDNA and proteins								
CancerSEEK tests: 8 proteins and ctDNA: CA-125, CEA, CA 19-9, PRL, HGF, OPN, MPO, TIMP-1	P	D	AV	59	99	NA	NA	[84]
Complement fragments								
C4d levels	P	D of IPN	AV	44	89	54	84	[85]
miRNA								
MILD trial study: 24 MSC	P	D, Pred	CV	87	81	27	99	[86]
13 signature miR-Test (COSMOS LCS programme): miR-92a-3p, miR-30b-5p, miR-191-5p, miR-484, miR-328-3p, miR-30c-5p, miR-374a-5p, let-7d-5p, miR-331-3p, miR-29a-3p, miR-148a-3p, miR-223-3p, miR-140-5p	S	HRP	CV	78	75	10	99	[87]
DNA methylation								
SOX17, TAC1, HOXA7, CDO1, HOXA9, ZFP42 methylation	P, Sp	D	AV	93–98	62–71	86–93	78–89	[88]
SHOX2 and PTGER4 methylation	P	D, D of IPN	CV	67	73	NA	NA	[89]
CDO1, HOXA9, AJAP1, PTGDR, UNCX and MARCH11 methylation	Mult	D, Prog	CV	72	71	82	51	[90]
AHRR (cg05575921) methylation	P	D	V	V	V	V	V	[91]

AAB: autoantibodies; AHRR: aryl hydrocarbon receptor repressor; AV: analytical validation; CEA: carcinoembryonic antigen; ctDNA: circulating tumour DNA; CV: clinical validation; D: diagnosis; DP: development phase; HRP: high-risk population; IPN: indeterminate pulmonary nodule; LCS: lung cancer screening; miRNA: microRNA; MSC: miRNA signature classifier; Mult: lung tissue, serum, pleural effusion, and ascites; NA: not available; NPV: negative predictive value; P: plasma; PPV: positive predictive value; Pred: prediction; Prog: prognosis; S: serum; Sp: sputum; V: various screening cohorts. Information from [46, 71].

signature classifier (MSC) and LDCT improved the accuracy of LDCT alone [86]. Further efforts have been made to combine radiological and blood-based biomarkers in LCS. The BIOMILD trial showed the combined use of LDCT and blood miRNAs at baseline can predict individual LC incidence and mortality with important implications in personalising LCS intervals [93]. On a similar background, other studies aim to develop and evaluate new blood tests for detecting cancer early and determine whether the addition of biomarkers to LDCT improves diagnostic performance in LCS [66, 94–96].

Radiomics in LCS

Radiomics is the extraction of data from medical imaging using mathematical algorithms for advanced image analysis and it does not necessarily require AI [97]. The selected features can be used for the subsequent mining of these data to improve decision support and nodule classification. Radiomics research is also evaluating ways in which it can be used for predicting prognosis or the probability of response to treatment of confirmed lung malignancies [97, 98]. Radiomic analysis relies on statistics, using various methods such as clustering or dimensionality reduction, random forest, linear regression and others.

There is immense potential in the use of radiomics in LCS with the view to differentiate benign from malignant LDCT detected nodules, as it could save unnecessary investigations and/or further radiological follow-up. Radiomics could be applied across the entire LC pathway from screening to diagnosis, staging treatment and follow-up [99, 100]. Promising perspectives arise from radiomics-based models in LCs, yet further data are required for their daily implementation. However, radiomics in LCS still lacks robust research and generalisability of the learned signatures to allow for application in daily clinical LCS services. Multicentric collaboration and attention to quality and reproducibility of radiomics studies should be further considered. The Image Biomarker Standardization Initiative validated consensus-based reference values for 169 radiomics features, thus enabling calibration and verification of radiomics software [101]. These reference values will increase reproducibility of radiomics studies and facilitate clinical translation of radiomics in LCS.

For instance, a LDCT-based radiomic model improved characterisation and screening recall intervals of indeterminate prevalent pulmonary nodules [102]. Moreover, radiomics analysis predicted pulmonary nodule malignancy using machine learning approaches [103]. Ongoing research aims to combine radiomics and blood biomarkers to augment incidental nodule stratification and identify high-risk patients who may benefit from more frequent surveillance or earlier diagnostics, and low-risk patients suitable for reduced surveillance intensity [104].

Artificial intelligence

AI is a branch of computer science that attempts to both understand and build intelligent entities, often instantiated as software programmes [105]. AI has been tested in various scenarios in LCS and early LC diagnosis.

A deep learning algorithm used patients' current and prior CT volumes to predict the risk of LC. It was tested and validated in NLST cases [106], reporting on the potential for deep learning models to increase the accuracy, consistency and adoption of LCS. Table 5 presents an overview of AI entities applicable in LCS and what they do.

AI modalities can offer automated analysis which allows more accurate characterisation of lung nodules and earlier detection of LC. For this to occur, radiological image data standardisation is required to ensure there is a valid application in real life clinical settings [98]. Computer aided diagnostics (CAD) has been used for automated lung nodule detection on CT scans for over 20 years and in some countries (*e.g.* the UK) it is mandated for nodule detection [107]. However, neither of the large LCS studies, NLST and the NELSON trial, used CAD for lung nodule detection [3, 4]. An ancillary study from the NELSON trial compared CAD and double reading by radiologists, in a cohort of 400 CT scans randomly selected from the NELSON database [108]. The sensitivity for lung nodule detection was 78.1% for double reading and 96.7% for CAD, at an average cost of 3.7 false-positive detections per examination. Visual confirmation remains necessary for reducing false positives when using a CAD for the detection of subsolid nodules [109].

Lung nodule volumetry of screen-detected nodules was assessed by CAD in the NELSON study to calculate volumetry-based doubling time. Volumetry software is less reliable for subsolid nodules, even though the doubling times of solid and nonsolid components of part-solid nodules can be separately estimated [98]. The use of lung nodule volumetry has been incorporated into some screening programmes [110].

The use of AI has the potential to improve LCS programmes efficiency, optimise radiology resources and assist in the LC diagnosis. It has been shown that training a deep learning algorithm on a LCS dataset can

TABLE 5 Artificial intelligence (AI) applications in lung cancer screening

AI entities	What do they do?
Machine learning [98]	A field of computer science It uses algorithms to identify patterns in data, such as the different imaging modalities It gives computers the ability to learn from data and reproduce human interpretations without being explicitly programmed
Deep learning [98, 105]	A subfield of the larger discipline of machine learning It employs artificial neural networks with many layers to identify patterns in data It is the state-of-the art in machine learning Strong points include classification, disease detection and segmentation
CNN [98]	They mimic the way the human brain processes information They combine multiple formal neurons, each of them processing part of the information, with their intelligent combination leading to the final decision rule
CAD [98]	Refers to tools developed to assist image reading Deep learning replaces the process of feature extraction and disease classification of the traditional CAD systems but it requires large datasets for training

CNN: convolutional neural networks; CAD: computer aided diagnosis.

result in cancer detection equivalent or higher than six radiologists when a single CT was analysed [98, 111]. This area is likely to continue to grow in academic research and implementation into routine clinical care. In an attempt to further optimise LCS outcomes, there are several ongoing LCS trials combining LDCT, blood-based biomarkers and AI such as the companion projects DART [112] and SCOOT [113] and their results are anticipated.

Implementation challenges in LCS

LCS implementation requires the careful consideration of several factors including the selection of high-risk individuals, screening delivery, delivery of addition services, such as smoking cessation, and management strategies for both malignant and incidental findings. Given the limited resources within a healthcare system, implementation can be hindered by several challenges that need to be considered in advance.

Participants' engagement and adherence

Participants' engagement and adherence to LCS is one of the biggest challenges and if not addressed it could compromise the entire LCS programme. High-risk individuals should be informed of the availability of LCS programmes, what they include, how they will access them, and what happens after screening. Screening participation should include an informed discussion of the risk and benefits derived from LCS.

Targeted campaigns or information provided by primary healthcare can contribute to sharing valuable information in lay language and avoid non-participation or non-adherence. Participant drop-out is usually due to knowledge avoidance, perceived low value, false-positive worry, practical barriers, or misunderstanding [114].

A targeted approach for "hard to reach" populations must be addressed in a tailored way to ensure participation. Patients who smoke experience the oxymoron of feeling stigmatised by their own choice to smoke while at the same time the absence of concerning symptoms makes it difficult for them to understand the necessity of LCS and this contributes to low participation rate [114, 115]. This effect is also seen in socioeconomically deprived groups with lower uptake of screening [114]. As these groups benefit significantly from screening, consideration of access should be made when implementing LCS programmes.

Healthcare professionals' availability and expertise

Availability is a main theme in primary care where the identification and recruitment of high-risk participants occur. General practitioners have limited time slots with short appointments to address active healthcare issues. It can be challenging to simultaneously relay information for LCS and devote the time to ensure the participant has made an informed decision. Dedicated clinic slots for LCS recruitment or targeted approaches to the high-risk population only could be a potential solution to overcome this barrier [116].

LCS programmes require the presence of experienced radiologists to report LCS imaging as well as radiographers to perform the scan with predefined technical standards [32] and administrative staff to support the service [114]. Expansion of LCS programmes will intensify the existing national shortages of chest radiologists and radiographers and needs to be an encountered challenge prior to LCS implementation [117].

Service capacity

LDCT scanner capacity can pose another challenge in LCS implementation especially where the same scanners are used for daily service provision for other services in addition to LCS [117]. The management of suspicious findings and indeterminate lung nodules reported by LCS adds to the above, as there is a need to increase capacity for these findings to be investigated and/or followed up as appropriate [115]. Standard protocols are required for managing all findings to avoid duplication of investigations and unnecessary clinic visits [39].

Access to smoking cessation

Smoking cessation services need to be embedded into LCS programmes to ensure screening benefit is optimised. The two main challenges relating to this are the availability of smoking cessation centres and that LCS participants may significantly overestimate the benefit of LCS over smoking cessation [118]. LCS participants may have misperceptions about the harm reduction itself as they feel that everyone who undergoes LCS will benefit regardless of smoking cessation [118]. Targeted short advice on smoking cessation is required during the enrolment of participants to ensure they understand the added benefit of smoking cessation to LDCT.

Conclusions

Early detection through LCS is crucial to improve population health outcomes. LCS through LDCT scans and smoking cessation has been shown to reduce LC mortality. National LCS programmes have started in a few countries but currently there are no uniform European guidelines for the definition of high-risk participants or inclusion in LCS. Further research is underway with regards to individual risk prediction models to help optimise inclusion in LCS. Blood-based biomarkers have already been available for LC diagnosis; however, they lack accuracy in the differentiation of indeterminate lung nodules into benign or malignant. Exciting advances in radiomics and AI may help in nodule assessment; however, they require prospective clinical evaluation prior to use in routine LCS programmes. LCS implementation poses challenges that should be considered in advance with management plans in place.

Key points

- National LCS programmes are still uncommon worldwide with only three within Europe.
- There are no set European guidelines for LCS. However, the European Respiratory Society has published technical standards for LCS and has provided a framework for the management of incidental findings.
- Several risk prediction models have been applied, with the CanPredict model showing higher sensitivity than the $PLCO_{m2012}$ model and LLP version 2 model.
- To date, there is no optimal biomarker to be integrated in LCS.
- Radiomics and AI can play a significant role in LDCT reporting and accurate diagnosis of indeterminate lung nodules.
- LCS implementation continues to face challenges that should be considered when initiating programmes.

Self-assessment questions

Please select all answers all that apply.

1. The following European countries have implemented a nationwide LCS programme until the end of 2023:
    a) France
    b) Poland
    c) Croatia
    d) Czech Republic
2. Most pilot and/or formal LCS programmes are based on the following two randomised clinical trials:
    a) LUST
    b) NLST
    c) MILD
    d) NELSON
3. There is a lack of consensus about the inclusion of the following in LCS programmes:
    a) age
    b) past cancer history
    c) nonsmoking women
    d) smoking history (pack-years)
    e) genetic predisposition for lung cancer
    f) occupational or environmental exposure to carcinogens

Conflict of interest: A. Frille reports receiving grants from “MetaRot program” fellowship from the Federal Ministry of Education and Research (BMBF), Germany (FKZ 01EO1501, IFB Adiposity Diseases): physician position, a junior research grant from the Medical Faculty, University of Leipzig (934100-012), a research grant from the “Mitteldeutsche Gesellschaft füür Pneumologie (MDGP) e.V.” (2018-MDGP-PA-002), and an unrestricted research grant by “Novartis Foundation”, outside the submitted work. F. Beyaz reports receiving a grant from the Dutch Cancer Foundation (KWF-grant number 14979), outside the submitted work. The remaining authors have nothing to disclose.

Support statement: A. Frille was supported by the postdoctoral fellowship “MetaRot program” (clinician scientist programme) from the Federal Ministry of Education and Research (BMBF), Germany (FKZ 01EO1501, IFB Adiposity Diseases), a research grant from the “Mitteldeutsche Gesellschaft für Pneumologie (MDGP) e.V.” (2018-MDGP-PA-002), a junior research grant from the Medical Faculty, University of Leipzig (934100-012), and a graduate fellowship from the “Novartis Foundation”.

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Suggested answers

1. b, c and d.
2. b and d.
3. b, c, e and f.