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Randomised controlled trials, including the National Lung Screening Trial (NLST) and the NELSON trial, have shown reduced mortality with lung cancer screening with low-dose CT compared with chest radiography or no screening. Although research has provided clarity on key issues of lung cancer screening, uncertainty remains about aspects that might be critical to optimise clinical effectiveness and cost-effectiveness. This Review brings together current evidence on lung cancer screening, including an overview of clinical trials, considerations regarding the identification of individuals who benefit from lung cancer screening, management of screen-detected findings, smoking cessation interventions, cost-effectiveness, the role of artificial intelligence and biomarkers, and current challenges, solutions, and opportunities surrounding the implementation of lung cancer screening programmes from an international perspective. Further research into risk models for patient selection, personalised screening intervals, novel biomarkers, integrated cardiovascular disease and chronic obstructive pulmonary disease assessments, smoking cessation interventions, and artificial intelligence for lung nodule detection and risk stratification are key opportunities to increase the efficiency of lung cancer screening and ensure equity of access.

Introduction

Lung cancer is the leading cause of cancer-related death globally.[1] Lung cancer screening is based on the premise that detection at an early stage reduces mortality. Indeed, clinical trials have demonstrated lower lung cancer-related mortality in patients screened with low-dose CT,[2,3] and increased detection of lung cancer at an early stage and reduction in later stage disease.[4] Available evidence has enabled some consensus on practice guidelines and the design of screening programmes; however, uncertainty remains about many aspects that might be essential to maximise the clinical effectiveness and cost-effectiveness of lung cancer screening while minimising the potential harms.

This review synthesises available evidence on lung cancer screening, including landmark clinical trials, identifying participants for screening, management of screen-detected findings, smoking cessation interventions, cost-effectiveness, personalised screening intervals, the potential of artificial intelligence and biomarkers, and an international perspective of current challenges and opportunities in lung cancer screening implementation.

Search strategy and selection criteria

We searched MEDLINE, Scopus, and the Cochrane Library, with no language restrictions, with the terms "lung cancer screening" and "lung screening", in combination with the terms "trial", "risk prediction", "risk models", "selection", "management", "guidelines", "follow-up", "incidental findings", "COPD", "cardiovascular risk", "smoking cessation", "tobacco cessation", "cost effectiveness", "screening interval", "artificial intelligence", "machine learning", "deep learning", "radiomics", "biomarkers", and "implementation". The most relevant clinical trials, systematic reviews and meta-analyses, other original research articles, and guidelines from January 1, 2000, to April 30, 2022, were included. References of initially identified articles were retrieved to identify additional relevant papers.

Clinical trials

Early clinical trials in the 1970s investigated the potential of chest radiography and sputum analysis for lung cancer screening.[5] These trials found no mortality benefit, leading to a slow down in related research in the 1980s. The first lung cancer screening trial using low-dose CT was done in Japan[6] and was followed by the Early Lung Cancer Action Project (ELCAP) in North America in the 1990s.[7] ELCAP demonstrated the superior ability of low-dose CT over chest radiography to detect small non-calcified nodules that might represent early-stage lung cancers.[7] Subsequently, two large randomised controlled trials were designed to determine the mortality impact of lung cancer screening with low-dose CT—the National Lung Screening Trial (NLST)[2] and the Nederlands Leuvens Screening Onderzoek (NELSON) trial.[3]

The NLST randomly assigned 53 454 individuals at high risk of lung cancer across 33 centres in the USA to three annual screenings with either low-dose CT or chest radiography between 2002 and 2004. In the low-dose CT group, there was a 20·0% relative reduction in mortality from lung cancer (95% CI 6·8–26·7; p=0·004) and a 6·7% reduction in all-cause mortality (95% CI 1·2–13·6; p=0·02) compared with the radiography group. The number needed to screen to prevent one lung cancer-related death was 320.[2]

The NELSON trial randomly assigned 13 195 men (primary analysis) and 2594 women (subgroup analysis) between 2003 and 2006 to undergo low-dose CT at baseline and at 1 year, 3 years, and 5·5 years, or no screening.[3] In contrast to the 2-dimensional (2D) diameter-based assessment of lung nodules that defined positive and negative scans in the NLST, the NELSON trial relied on semiautomated volumetric nodule measurements to guide management. The NELSON investigators found a 24% cumulative reduction in death from lung cancer at 10 years (cumulative rate ratio [RR] 0·76; 95% CI 0·61–0·94; p=0·01) in the screening group for men. The cumulative reduction among

	Recruitment period	Inclusion criteria	Primary comparison	Key outcomes
Randomised trials				
NLST[2]	2002–04	Age 55–74 years; ≥30 pack-year smoking history; currently smoke or quit <15 years ago	Annual low-dose CT *vs* chest radiography for 3 years (n=53 454)	20% reduction in lung cancer-related mortality with low-dose CT
NELSON[3]	2003–06	Age 50–74 years; >15 cigarettes per day for >25 years or >10 cigarettes per day for >30 years; currently smoke or quit ≤10 years ago	Low-dose CT at baseline and in year 1, year 3, and year 5·5 *vs* no screen (n=15 789)	24% reduction in lung cancer-related mortality with low-dose CT in men
AME[8]	2013–14	Age 45–70 years with at least one risk factor for lung cancer: (1) ≥20 pack-year smoking history and currently smoke or quit <15 years ago; (2) family history of cancer; (3) cancer history of any kind; (4) occupational exposure to carcinogenic agents; (5) long history of passive smoking; (6) long-term exposure to cooking oil fumes	Low-dose CT *vs* no screen; baseline low-dose CT and one repeat screen at 24 months (n=6657)	74% increase in detection of early-stage lung cancer with low-dose CT. A substantial proportion of the participants not meeting NLST criteria were diagnosed with lung cancer, suggesting that non-smoking-related risk factors need to be further explored in the Chinese population
DLCST[9]	2004–06	Age 50–70 years; ≥20 pack-year smoking history; currently smoke or quit <10 years ago; FEV_1 ratio >30%; able to climb two flights of stairs without pausing	Annual low-dose CT for 5 years *vs* no screen (n=4104)	No statistically significant difference in lung cancer-related mortality between the groups
MILD[10]	2005–18	Age 49–75 years; ≥20 pack-year smoking history; currently smoke or quit <10 years ago	Annual low-dose CT *vs* biennial low-dose CT *vs* no screen (median 7 annual low-dose CT or 4 biennial low-dose CT) (n=4099)	39% reduction in lung cancer-related mortality with either annual or biennial low-dose CT screening *vs* no screening
UKLS[11]	2011–13	Age 50–75 years; 5-year lung cancer risk ≥4·5% (LLP_{v2})	Low-dose CT (single screen) *vs* no screen (n=4055)	No statistically significant reduction in lung cancer-related mortality
LUSI[12]	2007–11	Age 50–69 years; ≥15 cigarettes/day for >25 years or ≥10 cigarettes/day for >30 years; currently smoke or quit ≤10 years ago	Annual low-dose CT and smoking cessation for 5 years *vs* smoking cessation alone (n=4052)	69% reduction in lung cancer-related mortality with low-dose CT in women. No statistically significant difference in lung cancer-related mortality in men
LSS[13]	2000–01	Age 55–74 years; ≥30 pack-year smoking history; currently smoke or quit <10 years ago	LDCT *vs* chest radiography; baseline and year 1 screen (n=3318)	No statistically significant reduction in lung cancer-related mortality (demonstrated feasibility to conduct the NLST trial)
ITALUNG[14]	2004–06	Age 55–69 years; ≥20 pack-year smoking history; currently smoke or quit <10 years ago	Annual low-dose CT for 4 years *vs* no screen (n=3206)	No statistically significant difference in lung cancer-related mortality
DANTE[15]	2001–06	Men, age 60–74 years; ≥20 pack-year smoking history; currently smoke or quit <10 years ago	Baseline low-dose CT then annual low-dose for 4 years *vs* no screen (n=2450)	No statistically significant reduction in lung cancer-related mortality with low-dose CT
Lung Screen Uptake Trial[16]	2015–17	Age 60–75 years; smoker within 7 years; ≥30 pack-year smoking history and currently smoke or quit within 15 years or 6-year lung cancer risk ≥1·51% ($PLCO_{m2012}$) or score ≥2·5% (LLP)	Provision of leaflet designed to target psychological barriers to participation *vs* standard recruitment approach (n=2012)	No statistically significant difference between intervention and control groups; however, higher participation rates than previous clinical and real-world studies, suggesting a stepped sequence of pre-invitation, invitation, and reminder letters from primary care practitioners and a so-called Lung Health Check approach might improve participation and reduce disparities, including in lower socioeconomic areas
Depiscan study[17]	2002–04	Age 50–75 years; ≥15 cigarettes/day for ≥20 years; currently smoke or quit <15 years ago	Baseline and annual low-dose CT *vs* chest radiography for 2 years (n=621)	Non-calcified nodules detected 10 times more often on low-dose CT than chest radiograph
4-IN-THE-LUNG-RUN[18]	2020–present	Age 60–79 years; ≥35 pack-year smoking history; currently smoke or quit less than 10 years ago or age ≤79 years and $PLCO_{m2012noRace}$ 6-year lung cancer risk >2·60%	Annual *vs* biennial screening for participants with normal baseline low-dose CT; n=24 000 (target)	Study is ongoing and final results are pending. The study will assess personalised risk-based screening intervals, personalised recruitment strategies, smoking cessation strategies, and cardiovascular disease and COPD prevention strategies
SUMMIT[19,20]	2019–present	Age 55–77 years; ≥30 pack-year smoking history (or at least 20 years duration) and currently smoke or quit <15 years ago or $PLCO_{m2012}$ 6-year lung cancer risk of ≥1·3%	Annual *vs* risk-targeted biennial screening for participants with normal baseline low-dose CT; n=25 000 (target)	Study is ongoing and final results are pending. Primary outcomes are to (1) evaluate the performance of a multi-cancer early detection blood test based on high-intensity sequencing of cell-free nucleic acids and (2) assess the implementation of low-dose CT for lung cancer screening in a high-risk population

(Table 1 continues on the next page)

	Recruitment period	Inclusion criteria	Primary comparison	Key outcomes
(Continued from previous page)				
Single-arm or cohort studies				
National Lung Cancer Screening programme cohort study[21]	2013–18	Age 40–74 years; at high risk of lung cancer based on a sex-specific scoring system derived from the Harvard Cancer Risk Index	Baseline (one-off) low-dose CT *vs* no screen (n = 1 016 740, including n=223 302 in the high-risk group)	One-off low-dose CT screening was associated with a 31% decrease in lung cancer mortality and a 32% decrease in all-cause mortality in China
ELCAP[7] and I-ELCAP[22]	1993–2005	Age ≥60 years and ≥10 pack-year smoking history (ELCAP); age ≥40 years who currently smoke or previously smoked, had exposure to second-hand smoke, or had occupational exposure to asbestos, beryllium, uranium, or radon (I-ELCAP)	Baseline screening (n=31 567), followed by annual repeat screening (n=27 456)	Annual low-dose CT screening can detect lung cancer that is curable (85% of screen-detected lung cancers were stage I with an estimated 10-year survival rate of 88%)
TALENT[23]	2015–19	Age 55–75 years, never smoked, and with one of the following risk factors: family history of lung cancer within third-degree, passive smoking exposure, tuberculosis/COPD, cooking index ≥110, and not using ventilator during cooking	Baseline low-dose CT, annual low-dose CT for 2 years and biennial low-dose CT for 6 years if no lung cancer is detected (n=12 011)	Baseline lung cancer detection rate in a high-risk population who had never smoked in Taiwan was 2·6%, higher than found in the NLST and NELSON studies. Final trial results are pending
ILST[24,25]	2015–20	Age 55–80 years, currently smoke or previously smoked and met USPSTF (2013) criteria or 6-year lung cancer risk ≥1·51% ($PLCO_{m2012}$)	Baseline low-dose CT and one repeat in 1–2 years (n=5819)	$PLCO_{m2012}$ might be more efficient than the USPSTF (2013) criteria for identifying high-risk individuals for lung cancer screening. Final trial results are pending
K-LUCAS[26]	2017–18	Age 55–74 years; ≥30 pack-year smoking history; currently smoke or quit <15 years ago	Baseline low-dose CT and one repeat in 1 year (n=5692)	A national lung cancer screening in an Asian population is feasible to detect early-stage lung cancer and promote smoking cessation
Manchester Lung Health Check[27]	2016–17	Age 55–74 years; 6-year lung cancer risk ≥1·51% ($PLCO_{m2012}$)	Annual low-dose CT over two screening rounds (n= 2541)	Mobile CT scanners adjacent to shopping centres could help effectively engage high-risk individuals in deprived areas. Terminology of "lung health check" rather than "lung cancer screening" might improve participation
PanCan[28]	2008–10	Age 50–75 years; 6-year lung cancer risk ≥2% (PanCan)	Low-dose CT screening at baseline, year 1, and year 4 (n=2537)	The PanCan model was more effective in identifying individuals who were subsequently diagnosed with stage I lung cancer compared with NLST criteria
Liverpool Healthy Lung Programme[29]	2016–18	Age 58–75 years with a history of smoking or a diagnosis of COPD; 5-year lung cancer risk ≥5% (LLP)	Annual low-dose CT (n=1318 for baseline CT)	A proactive community-based approach in health-deprived regions or areas is likely to be effective in the early diagnosis of lung cancer
COSMOS[30]	2000–01	Age >50 years; >20 pack-year smoking history	Annual low-dose CT for 10 years (n=1035)	Neither cancer frequency nor proportion of cancers at stage I decreased over 10 years, suggesting that screening should continue beyond 10 years

4-IN-THE-LUNG-RUN=Towards Individually Tailored Invitations, Screening Intervals and Integrated Co-morbidity Reducing Strategies in Lung Cancer Screening. COSMOS=Continuous Observation of Smoking Subjects. COPD=chronic obstructive pulmonary disease. DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology. DLCST=Danish Lung Cancer Screening Trial. ELCAP=Early Lung Cancer Action Project. I-ELCAP= International Early Lung Cancer Action Project. ILST=International Lung Screening Trial. ITALUNG=Italian Lung Cancer Screening Trial. K-LUCAS=Korean Lung Cancer Screening Project. LLP=Liverpool Lung Project criteria. LSS=Lung Screening Study. LUSI=Lung Cancer Screening Intervention. MILD=Multicentric Italian Lung Detection trial. NELSON=Nederlands Leuvens Screening Onderzoek trial. NLST=National Lung Screening Trial. PanCan=Pan-Canadian Early Detection of Lung Cancer Study. PLCO=Prostate Lung Colorectal and Ovarian study model. SUMMIT= Cancer Screening Study with or without Low Dose Lung CT to Validate a Multicancer Early Detection Test. TALENT=Taiwan Lung Cancer Screening for Never Smoker Trial. UKLS=United Kingdom Lung Cancer Screening Trial. USPSTF=United States Preventive Services Task Force.

Table 1: **Clinical trials of lung cancer screening with low-dose CT**

women was even higher at 33%, although there was insufficient power to show a significant result (cumulative RR 0·67; 95% CI 0·38–1·14). Unlike the NLST, the NELSON trial did not find a statistically significant difference in all-cause mortality between the screening and no screening groups at 10 years. Only 16% of trial participants in the NELSON trial were women, and although women were not included in the primary analysis, they were included in a subgroup analysis.[3] Several smaller European trials have also been done (table 1) and contribute to evidence about participant recruitment strategies, adherence, and cost-effectiveness in different settings. A meta-analysis including 94 921 participants from nine randomised controlled trials showed a 16% relative reduction in lung cancer mortality (relative rate 0·84; 95% CI 0·76–0·92) and a 3% relative reduction in all-cause mortality (RR 0·97; 95% CI 0·94–1·00) with low-dose CT screening.[11] A 2021 population-based, prospective cohort study from China with 1 016 740 participants found that one-off low-dose CT screening was associated with a 31% decrease in lung cancer mortality (hazard ratio 0·69; 95% CI 0·53–0·92) and a 32% decrease in all-cause mortality (hazard ratio 0·68; 95% CI 0·57–0·82).[21]

Identifying participants for lung cancer screening

Identifying high-risk individuals

Lung cancer screening is considered most effective in individuals at high risk for lung cancer, and several approaches exist to identify high-risk individuals. The NLST and NELSON studies used relatively simple, categorical criteria to define high risk. The NLST included individuals aged 55–74 years with a smoking history of at least 30 pack-years and, if they had quit smoking, had done so within the past 15 years.[2] The NELSON trial included individuals aged 50–74 years, with a smoking history of more than 15 cigarettes per day for more than 25 years or more than ten cigarettes per day for more than 30 years and, if they had quit smoking, had quit within the past 10 years.[3]

The NLST selection criteria have been incorporated with minor variations into screening guidelines across several countries (table 2). The United States Preventive Services Task Force (USPSTF) recently expanded eligibility to include people aged 50–80 years and a smoking history of 20 pack-years.[34] A subsequent update to the national coverage decision from the United States Centers for Medicare & Medicaid Services similarly expanded eligibility criteria for Medicare beneficiaries.[45] The expanded criteria allow more people to benefit from screening, including a greater number of women and minority racial or ethnic groups who may develop lung cancer with lower smoking histories.[34,46,47] Modelling studies have shown that a screening programme based on the revised criteria would reduce lung cancer mortality by 13·0%, compared with 9·8% based on the 2013 criteria.[48] Black men in the USA have a higher incidence of lung cancer and higher mortality from lung cancer, and racial minorities and women develop lung cancer at an earlier age and with lower smoking histories than White men.[46,49] The revised criteria would increase the relative proportion of non-Hispanic Black adults who are eligible for lung cancer screening by 107% (from 1·9% to 3·9%), compared with an increase of 87% for the population overall, which could help to partially reduce racial disparities in health outcomes.[34]

An alternative approach has been to develop multivariable mathematical models that estimate lung cancer risk over a specified period and choose a risk threshold to determine eligibility. Two risk models have been particularly well evaluated and used in screening trials: the Prostate, Lung, Colorectal and Ovarian (PLCO) model and the Liverpool Lung Project (LLP) model.[50–52] The PLCO model was developed using data from the PLCO screening trial.[53,54] This model was subsequently updated to the $PLCO_{m2012}$ model,[50] which considers age, race, smoking history, personal history of cancer, family history of lung cancer, presence of chronic obstructive pulmonary disease (COPD), education level, and body-mass index.[50] In retrospective analyses of the PLCO and NLST, the $PLCO_{m2012}$ risk model outperformed the USPSTF criteria for accuracy of lung cancer risk prediction.[50] The $PLCO_{m2012}$ model has been prospectively evaluated in the International Lung Screening Trial, a prospective cohort study which aimed to compare the accuracy of the $PLCO_{m2012}$ model to the USPSTF criteria, and to evaluate a nodule management strategy based on a nodule malignancy probability calculator (PanCan model) compared with American College of Radiology's Lung CT Screening Reporting and Data System (Lung-RADS).[24] At a threshold risk of at least 1·51% within 6 years, the $PLCO_{m2012}$ model showed greater predictive ability than the USPSTF criteria for lung cancer incidence in 5819 participants.[25]

The LLP risk model was developed in 2008 based on data from a case-control study with 1736 participants in Liverpool, UK.[51] Updated versions 2 (LLP_{v2})[52] and 3 (LLP_{v3})[55] consider age, sex, smoking history, personal history of cancer, family history of lung cancer, exposure to asbestos, and history of pneumonia, emphysema, bronchitis, tuberculosis, and COPD.[55] The LLP_{v2} model was used to determine eligibility for the United Kingdom Lung Screen (UKLS) trial at a threshold of 5% over 5 years and showed a 2·1% detection rate after a single low-dose CT screen.[51,52]

Two studies comparing the predictive ability of up to nine lung cancer risk models found that the $PLCO_{m2012}$ model demonstrated the best discrimination based on data from the European Prospective Investigation of Cancer and Nutrition-Germany cohort[56] and NLST and PLCO cohorts.[57] A 2021 study found the Lung Cancer Death Risk Assessment Tool (LCDRAT) and Lung Cancer Risk Assessment Tool (LCRAT) to have the best discrimination, with areas under the receiver operating characteristic curve (AUC) of 0·82 and 0·81, respectively, outperforming the $PLCO_{m2012}$ and LLP_{v3} models.[58] A 2018 study which compared nine lung cancer risk models similarly found the LCDRAT, LCRAT, and $PLCO_{m2012}$ models to have the best discrimination.[59]

In Korea, where categorical selection criteria for lung cancer screening similar to NLST have been used since 2019, a 2021 study explored risk models which might be more appropriate for Asian populations.[60] Lung cancer risk criteria in the National Health Insurance Service dataset combined with lung cancer incidence data from the Korea Central Cancer Registry in 969 351 individuals (70% of whom were in the training dataset, and 30% in the validation dataset) contributed to the development of a risk model that reflected the effects of factors such as existing lung disease, in particular interstitial lung disease.[60] The Korean model showed better discrimination and calibration than models developed in North American and European populations, including the $PLCO_{m2012}$ model, highlighting the importance of using geographically specific risk models.

Screening of people who have never smoked

Whereas the risk assessments outlined in the previous section focus on tobacco exposure, at least a quarter of

	Country/ region	Year	Recommended criteria
UK National Screening Committee[31,32]	UK	2022	Age 55–74 years with a history of smoking and determined to be at high risk of lung cancer (note: NHS England Targeted Lung Health Check Programme eligibility based on $PLCO_{m2012}$ risk of ≥1·51% over 6 years or LLP_{v2} 5-year risk of ≥2·5%)
Australian Medical Services Advisory Committee[33]	Australia	2022	Biennial screening with low-dose CT for adults aged 50–70 years with ≥30 pack-year smoking history who currently smoke or have quit within the past 10 years
United States Preventive Services Task Force[34]	USA	2021	Annual screening with low-dose CT in adults aged 50–80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years
Croatian Health Ministry[35]	Croatia	2020	Screening with low-dose CT in adults aged 50–70 years who have a 30 pack-year smoking history and who currently smoke or have quit within the past 15 years
German Radiological Society and the German Respiratory Society[36]	Germany	2019	Asymptomatic individuals at risk, age 55–74 years with a history of ≥30 years of smoking and fewer than 15 years since smoking cessation; and asymptomatic persons ≥50 years of age and history of ≥20 years of smoking and at least one of the following risk factors: history of lung cancer, family history of lung cancer, history of malignant ear, nose, or throat tumour or other malignant tumour associated with smoking, history of lymphoma, exposure to asbestos, chronic obstructive pulmonary disease, or pulmonary fibrosis
Academy of Medicine, Singapore[37]	Singapore	2019	Annual screening with low-dose CT in individuals aged 55–74 years with ≥30 pack-year smoking history who currently smoke or quit <15 years ago
Agency of Medical Technology Assessment[38]	Poland	2019	Annual screening with low-dose CT in individuals age 55–74 years with ≥20 pack-year smoking history who currently smoke or quit <15 years ago, or age 50–74 years if an additional risk factor is present
China Lung Cancer Early Detection and Treatment Expert Group[39]	China	2018	Annual screening with low-dose CT for adults age 50–74 years who have ≥20 pack-year smoking history and who currently smoke or have quit within the past 5 years
Saudi Lung Cancer Association of Saudi Thoracic Society[40]	Saudi Arabia	2018	A national lung cancer screening programme is not supported
European Union Lung Cancer CT Screening Implementation Group[41]	European Union	2017	No specific recommendation on screening eligibility, but should use a validated risk stratification approach (eg, $PLCO_{m2012}$ or the LLP_{v2}) so that only individuals at high risk are screened
Canadian Task Force on Preventive Healthcare[42]	Canada	2016	Annual screening with low-dose CT for up to 3 consecutive years in adults aged 55–74 years with at least a 30 pack-year smoking history, who currently smoke or have quit within the past 15 years
Korean Multisociety Collaborative Committee[43]	Korea	2015	Adults aged 55–74 years with a ≥30 pack-year smoking history and who currently smoke or have quit within the past 15 years
Japan Radiological Society and the Japanese College of Radiology[44]	Japan	2013	Low-dose CT screening for lung cancer for people aged ≥50 years with a Brinkman index ≥600 (comparable with ≥30 pack-year smoking history)

LLP_{v2}=Liverpool Lung Project risk prediction model version 2. NHS=National Health Service. $PLCO_{m2012}$= Prostate, Lung, Colorectal and Ovarian risk prediction model version m2012.

Table 2: **Recommended eligibility criteria for lung cancer screening with low-dose CT**

people with lung cancer worldwide have never smoked.[61] The prevalence of lung cancer in women who have never smoked is highest in south Asia (with 83% of women with lung cancer having never smoked) followed by east Asia (61%), but only 15% of women with lung cancer in the USA have never smoked.[61] Therefore, screening based on risk models developed elsewhere could miss many individuals who could benefit from early detection and curative treatment.[62] Analyses of Asian screening cohorts have shown that the incidence of lung cancer in people who have never smoked might not be far below that in people who have smoked. A retrospective analysis of 28807 Koreans who had undergone lung cancer screening with low-dose CT between 2003 and 2016 (42% of whom had never smoked, and 58% of whom had ever smoked) reported screen-detected lung cancer in 0·45% of individuals who had never smoked versus 0·86% of those who had ever smoked.[63] Conversely, a prospective analysis of 12114 Japanese people who underwent lung-cancer screening with low-dose CT between 2004 and 2012 (50% of whom had never smoked, 31% of whom had smoked with <30 pack-years, and 19% of whom had smoked with ≥30 pack-years) reported screen-detected lung cancer in 1·1% of those who never smoked compared with 1·1% of those who smoked.[64]

In 12011 people in Taiwan who had never smoked but had other risk factors for lung cancer (age 55–75 years, family history of lung cancer, passive smoking exposure, tuberculosis or COPD, high cooking index, and not using ventilation when cooking), low-dose CT detected lung cancer in 2·6% of participants,[23] which was higher than the rate of 1·1% detected in the first round of the NLST.[65] Even if the benefits of lung cancer screening in never smoking North American and European populations seem to be remote,[66] the high risk of lung cancer among Asian people who have never smoked suggests that Asian-specific

risk models are necessary to optimise eligibility for lung cancer screening. As screening eligibility criteria are optimised, care must be given to minimise overdiagnosis—the diagnosis of a lung cancer that would not cause symptoms or death—as it has been suggested that a substantial portion of lung cancers diagnosed in non-smoking Asian women might represent overdiagnosis.[67,68]

Occupational and environmental risk factors, including exposure to radon (which is present in soil and might be concentrated in mines and homes), asbestos, chromium, arsenic, and air pollution should also be considered to effectively identify individuals at high risk for lung cancer, as well as inform primary prevention programmes.[47,69] Risk factors for lung cancer can differ between men and women, suggesting strategies to identify high-risk individuals for lung cancer screening might need to be tailored for each sex. Although it has been shown that women with similar smoking histories have higher lung cancer susceptibility than men, studies are conflicting.[70–72] Differences in lung cancer epidemiology between men and women could be related to genetic variants, hormones, environmental exposures, and oncogenic viruses such as human papillomavirus but remain incompletely understood.[70,71]

Screening of cancer survivors

Survivors of prior lung and other cancers are at higher risk of developing a primary lung cancer than the general population.[73–76] Therefore, the merits of screening cancer survivors—who might not otherwise meet criteria for lung cancer screening—must be carefully considered.

Based on an analysis of US Surveillance, Epidemiology, and End Results Program data, among adult patients diagnosed with one of the ten most common primary malignancies, 8·1% developed a second primary malignancy, the most common of which was lung cancer.[73] The 10-year cumulative risk of a second primary malignancy among patients with a history of bladder cancer (the cancer type with the highest risk of a second primary malignancy) was 19%, with lung cancers comprising 25% of second primary malignancies.[73]

Among lung cancer survivors, the estimated 10-year risk of developing a second primary lung cancer was a median of 8·4% but with substantial variation according to age, histology, and the extent of the primary lung cancer.[74] These rates of lung cancer diagnoses are higher than in previous lung cancer screening studies that selected participants based on age and smoking history,[2,3] suggesting that cancer survivors might be at a sufficiently high risk of lung cancer to undergo screening, even if they do not meet current eligibility criteria based on their age and smoking history. However, cancer survivors form a heterogeneous population with various cancer types, demographics, and life expectancies, which hampers simple lung cancer screening guidelines in this setting.[77]

Existing guidelines for imaging surveillance of lung cancer survivors suggest chest CT every 6 months for the first 2–3 years after completion of treatment, followed by annual surveillance.[78–80] Although many guidelines do not specify the time period at which surveillance imaging should be discontinued, registry data from England suggest that lung cancer survivors remain at an increased risk of a smoking-related second primary cancer for at least 10 years from first lung cancer diagnosis, and that routine lung cancer follow-up should continue for 10 years.[75] Registry data from England and Germany suggest that cancer survivors are at risk not only for a secondary primary lung cancer, but also other smoking-related second primary cancers including head and neck, laryngeal, and oesophageal squamous cell carcinoma.[75,76]

Research is required to develop consensus surrounding lung cancer screening for lung cancer survivors and survivors of other cancers.

Management of screen-detected findings

Benefits need to outweigh harms in any screening programme. In lung cancer screening with low-dose CT, potential physical and psychological harm is mainly related to the detection and work-up of non-specific lung nodules and incidental findings. Lung cancer screening also provides an opportunity to assess for COPD and cardiovascular disease. Various guidelines have been introduced to standardise the reporting and management of screen-detected findings, and these guidelines might reduce both harms and costs.

Lung nodules and lung cancer

The management of lung nodules has evolved during the past four decades and is based on nodule size, morphology, location, and change over time (figure).[81,82] Lung-RADS

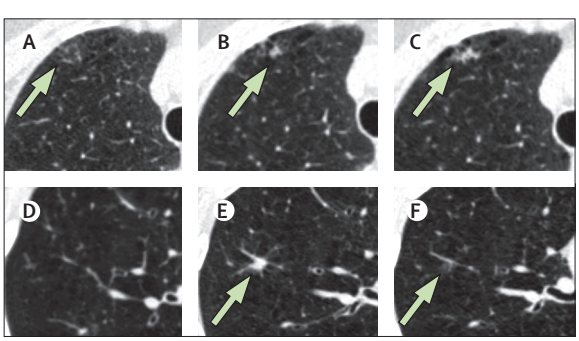

Figure: **Lung nodules identified on lung cancer screening low-dose CT in two patients**
(A–C) Patient 1. 62-year-old woman, current smoker with 72 pack-year smoking history and chronic obstructive pulmonary disease. Baseline low-dose CT (A) does not show a nodule (arrow). Annual low-dose CT at 15 months (B) shows a new right upper lobe solid nodule adjacent to emphysema (arrow) which increased in size to 17 × 8 mm (arrow) on the annual low-dose CT at 24 months (C). The patient underwent right upper lobectomy with a diagnosis of squamous cell carcinoma (T1aN0). (D–F) Patient 2. 60-year-old woman, current smoker with 40 pack-year smoking history. Baseline low-dose CT (D) does not show a nodule. Annual low-dose CT at 18 months (E) shows a new right upper lobe spiculated solid 9 × 6 mm nodule (arrow) which resolved on follow-up low-dose CT 3 months later (F, arrow), consistent with an inflammatory nodule.

2022 (released in November, 2022),[82] and British Thoracic Society (BTS) guidelines[81] attempt to incorporate these principles. Nodules can be solid, where none of the bronchovascular structures can be seen through the nodule, pure ground glass (or non-solid), where bronchovascular structures are visible through the nodule, or part solid, where the nodule has both a solid and a ground glass component.[83] Nodules close to the pleura can be classified as perifissural or subpleural, both usually benign and representing lymphoid tissue.[84] Nodules or irregularity in the wall of or in contact with cystic airspaces might represent cancer.[85,86]

The primary aim in lung nodule management is to distinguish, as soon as possible, nodules that are clinically relevant lung cancers from those that are either benign or indolent lung cancers. Nodule size and growth are the most important predictors of malignancy,[87] although guidelines differ regarding the measurement of these parameters.[41,81,82] Nodule size is either measured manually using electronic callipers or by semiautomated or fully automated segmentation. The error associated with manual measurements is believed to be 1·5 mm, which can amount to a substantial change in volume for small nodules.[88] For example, if a nodule were to change in diameter from 5 mm to 6 mm over 3 months, still falling below the cutoff for diameter growth, the volume doubling time would be 115 days, a rate consistent with a potentially lethal malignancy.[89] For this reason, semiautomated volumetry has been developed. The BTS guideline indicates that at least a 25% change in volume is required to be clinically significant (the diameter of a round 5 mm nodule would need to increase to 5·4 mm). Volumetry is now integrated into the BTS guideline, the subsequent European Position Statement, and the most recent version of Lung-RADS.[41,81,82]

Guidelines differ regarding the use of multivariable prediction models and PET-CT to evaluate the risk of malignancy of solid nodules. BTS recommends use of the PanCan/Brock University tool to assess risk at baseline CT for nodules at least 8 mm diameter or 300 mm³ in size and, if the chance of malignancy is greater than 10%, to use a further model (Herder) after PET-CT.[90,91] For nodules smaller than 8 mm, PET-CT is considered to have low accuracy for the characterisation of lung nodules.[81]

General agreement exists that sub-solid nodules (the group term for part solid and pure ground glass nodules) require a more conservative approach because sub-solid nodules are often indolent cancers and contribute to overdiagnosis.[41,81,82] Thus, pure ground glass nodules almost always undergo observation initially, with diagnosis and treatment considered only if a solid component develops. Part-solid nodules usually undergo observation initially unless the solid component measures 8 mm or greater, at which point PET-CT can be considered before biopsy or treatment.[81]

The overall aim of the workup following referral for suspected cancer is to quickly and safely confirm the diagnosis, complete tumour staging, and assess the patient's fitness for treatment. Cancers that are likely to reduce life expectancy should be treated, whereas individuals with benign or indolent disease should be reassured and return to the screening programme.

Guidelines recommend transthoracic needle biopsy for indeterminate probability nodules (10–70% BTS guideline or 10–60% American College of Chest Physicians),[81,92] with resection favoured for nodules with a high malignancy risk. Prompt tissue diagnosis might avoid stage progression, which could affect the overall treatment success.[93]

Differences in health-care systems drive different approaches to investigation and treatment, and lung cancer screening trials differ substantially in the number of investigations performed. For example, the proportion of those with surgical resection who turned out to have benign disease was 24% in the NLST,[2] but only 4·6% when the UKLS trial was combined with additional screening studies and pilots in the UK.[94] This improvement might be due to the implementation of the BTS nodule guidelines in 2015 complementing the existing National Institute for Health and Care Excellence lung cancer guidelines.[95]

Incidental findings

Incidental findings—imaging findings other than lung nodules—are often identified on lung cancer screening low-dose CT scans. One study found that incidental findings were reported in 28–67% of lung cancer screening participants, depending on whether they were imaged at a university imaging centre (67%) or at a community imaging centre (28%).[96] Another study found that although incidental findings were reported on 94% of such scans, only 15% of scans showed an incidental finding that resulted in further evaluation.[97] Incidental findings can lead to increased patient anxiety, radiation exposure from follow-up imaging, complications from work-up or treatment, and health system costs.[98] The potential risks associated with work-up of incidental findings should be balanced with the potential benefits, and appropriate management protocols for incidental findings are critical (table 3).

COPD assessment

Lung cancer screening is an opportunity to diagnose COPD. At least mild emphysema was detected on low-dose CT in 24–63% of screening participants, depending on screening inclusion criteria.[100–103] Findings from NLST and NELSON subcohorts suggest that quantifiable imaging biomarkers have reasonable sensitivity and specificity for COPD, even without lung function testing.[104–106] Most, but not all, screening studies have found that CT-derived emphysema is independently related to increased lung cancer risk,[106–108] with a relative risk of 1·3–3·6 merely for the presence of emphysema. Additionally, the presence and extent of emphysema

elevates the risk of all-cause, lung cancer, and respiratory mortality.[106,109] The importance of COPD within the context of lung cancer screening is not so much related to early intervention (currently comprising extra emphasis on smoking cessation), but to the possible value for selecting screening cohort, and potentially customising the frequency and duration of screening after the baseline low-dose CT. Combined screening criteria based on age and smoking history miss an important proportion of individuals who will suffer from lung cancer, in part due to suboptimal consideration of COPD.[110,111] The information on the baseline screening low-dose CT might also help to determine the risk of competing causes of death, which may lead to re-evaluation of screening benefit in participants with extensive emphysema.[112]

Cardiovascular risk assessment

The NLST and NELSON trials have shown that death from cardiovascular disease is a risk equal to or higher than death from lung cancer.[2,3] Cardiovascular risk assessment allows for early preventive treatment like statin therapy. Screening of individuals at high lung cancer risk on the basis of age and smoking history is therefore an opportunity to also identify those at highest risk of cardiovascular disease, potentially increasing the efficiency of low-dose CT screening.[113] One way of determining cardiovascular disease risk in screening participants is cardiovascular risk scoring based on risk factor self-report.[114,115] A UK-based investigation in a lung screening cohort[114] showed that 98% of participants without a history of cardiovascular disease were estimated to be at high cardiovascular risk (≥10% 10-year risk), with 57% of participants who qualified for primary cardiovascular prevention therapy with statin treatment not taking a statin. Another study[115] found that 93% of participants without a history of cardiovascular disease were estimated to be at high cardiovascular risk, of whom 47% were not on statin therapy. Many more studies have focused on the potential of cardiovascular risk information in the low-dose CT scan itself, based on the severity of coronary calcification. Due to the population included in lung cancer screening with a heavy smoking history, coronary calcium is noted on most lung cancer screening low-dose CT scans.[114–117] Coronary calcium can be quantified visually as aggregate (none, mild, moderate, or severe) or per coronary artery, or segmented and expressed as the Agatston score.[117–119] Studies show that more extensive coronary calcium, either by visual assessment or calcium scoring, is a strong predictor of cardiovascular events.[116,117,120,121] Two consensus documents now recommend standard reporting of coronary calcium on chest CT (including lung cancer screening low-dose CT) using a simple, visual assessment.[119,122] In the near future, deep-learning methods will likely be able to automate calcium scoring, which will reduce strain on radiologists' workload.[123] Whether or not coronary calcium-based management decreases cardiovascular

	Suggested recommendation for management
Neck	
Thyroid nodule (≥15 mm or with suspicious features)	Thyroid ultrasound and clinical evaluation
Thorax	
Coronary artery calcifications	Primary care evaluation for atherosclerotic cardiovascular disease risk assessment
Aortic valve calcification (moderate or greater)	Primary care evaluation
Enlarged main pulmonary artery (≥31 mm)	Primary care evaluation; consider cardiology or pulmonary consultation
Thoracic aortic aneurysm (ascending aorta ≥42 mm)	Primary care surveillance or cardiology consultation for aneurysm surveillance
Pericardial effusion (moderate or large)	Discuss with primary care provider
Mediastinal lymph nodes ≥15 mm in short axis and no explainable cause	Primary care evaluation; consider pulmonary consultation. Consider follow-up chest CT in 3–6 months
Mediastinal mass (soft tissue or mixed density)	Chest MRI or CT
Oesophageal focal wall thickening or mass	Primary care evaluation; consider gastroenterology consultation
Fibrotic interstitial lung disease	Recommend pulmonary consultation
Pleural effusion, thickening, or mass	Primary care evaluation; consider pulmonary consultation
Breast mass or asymmetric density	Diagnostic mammogram with or without ultrasound
Abdomen	
Hepatic lesion	Simple cyst or nodule <1 cm: no follow-up generally necessary; hepatic soft tissue mass ≥1 cm: abdominal CT or MRI
Fatty liver disease, hepatic steatosis, or cirrhosis	Primary care evaluation
Pancreatic cyst or mass	Abdominal CT or MRI
Adrenal nodule	Nodule <10 Hounsfield units (fat density): likely an adenoma with no follow-up necessary; soft tissue density nodule <1 cm or nodule stable ≥1 year: no follow-up generally necessary; other adrenal nodules or masses: adrenal CT or MRI
Simple or hyperdense/ haemorrhagic renal cyst (Bosniak I or II) <4 cm	No follow-up generally necessary
Soft tissue density (or mixed density) renal mass	CT or MRI of the kidneys
Musculoskeletal	
Osteopenia (100–130 Hounsfield units at L1)	Consider primary care evaluation
Osteoporosis (<100 Hounsfield units at L1)	Primary care evaluation and consider dual-energy x-ray absorptiometry

Adapted from the American College of Radiology Lung Cancer Screening CT Incidental Findings Quick Reference Guide.[99]

Table 3: **Management of selected incidental findings on low-dose CT lung cancer screening based on recommendations from the American College of Radiology[99]**

disease morbidity and mortality is being investigated in the ROBINSCA trial.[124]

Smoking cessation interventions

Smoking cessation is the most effective intervention in reducing lung cancer-related mortality, and lung cancer screening provides many opportunities to support individuals in quitting smoking.[125,126] Combining low-dose CT with effective smoking cessation programmes optimises the morbidity and mortality benefit of lung cancer screening programmes by reducing the risk of lung cancer and other tobacco-related diseases including COPD, cardiovascular disease, and other cancers, and has been shown to improve the cost-effectiveness of screening.[127,128]

Among lung cancer screening trial participants who currently smoke, 55–74% reported that participation in lung cancer screening increased their motivation for quitting smoking or attributed quitting to screening.[129–131] An analysis of NLST data found that smoking cessation was statistically significantly associated with a screen-detected abnormality, suggesting that abnormal screening results might represent a so-called teachable moment that supports smoking cessation.[132] Smoking cessation rates range from 7% to 23% in lung cancer screening trials; however, randomised controlled trials including NELSON, UKLS, and the Italian Lung Screening Trial (ITALUNG) offer contradictory results regarding whether or not participation in lung cancer screening itself supports smoking cessation.[131]

Studies of smoking cessation interventions have shown that intensive interventions such as multiple counselling sessions with or without pharmacological therapies might be most effective, with less intensive interventions such as providing brochures or performing brief counselling having a smaller effect on smoking cessation rates.[133] However, no consensus currently exists regarding optimal smoking cessation interventions, including their type and frequency, the content of messaging, and how they should best be integrated with communication of low-dose CT findings.[131,133] Several clinical trials are ongoing to address some of these knowledge gaps, including the Yorkshire Enhanced Stop Smoking (YESS) study and eight clinical trials comprising the Smoking Cessation within the Context of Lung Cancer Screening (SCALE) collaboration.[134,135] The YESS study—integrated within the Yorkshire Lung Screening Trial as a co-located service—aims to assess the efficacy of a personalised paper-based booklet that incorporates the participant's own low-dose CT images and a smoking cessation practitioner who highlights the short-term and long-term benefits of smoking cessation.[134] The clinical trials in the SCALE collaboration assess various smoking cessation intervention strategies of different intensities, including counselling (on-site and quit lines), pharmacotherapy, web-based programmes, text messaging, and gain versus loss message framing.[135] The Georgetown Lung Screening, Tobacco, and Health Project—one of the SCALE trials—randomly assigned 818 participants to intensive intervention (8 phone sessions and 8 weeks of nicotine patches) or minimal intervention (3 phone sessions and 2 weeks of nicotine patches) groups. Recently reported results showed that bio-verified quit rates were statistically significantly higher in participants in the intensive group at 3 months (9·1% *vs* 3·9%), but no statistically significant difference was found between the two groups at 6 months or 12 months.[136] Further research is needed to identify effective strategies to sustain smoking abstinence.

Cost-effectiveness

The reported cost-effectiveness of lung cancer screening has hampered its implementation in many countries. The range of cost estimates in the literature is broad, from US$1464 to $2 million per quality-adjusted life year (QALY) gained depending on the setting, modelling approach, and policy question.[137] A seminal paper based on an analysis of the NLST and 2009 Medicare prices found incremental cost-effectiveness ratios (ICERs) of $52 000 per life-year gained and $81 000 per QALY gained.[138] More recently, a comparative modelling study in 2021 found that the 2021 USPSTF recommendation was cost-effective compared with the 2013 USPSTF recommendation, with an ICER of $72 564 per QALY gained. However, the 2021 USPSTF strategy could be further optimised by including individuals who had quit smoking more than 15 years ago.[139] Another comparative modelling study found that although increasing the maximum age for lung cancer screening led to a greater reduction in mortality, it also led to higher costs and overdiagnosis, with ICERs averaging $49 200, $68 600, and $96 700 per QALY if stopping screening at age 74 years, 77 years, and 80 years, respectively.[140]

A Dutch study in people with heavy smoking histories found ICERs of €27 600 and €21 100 per life-year gained for men and women, respectively, compared with no screening.[141] In comparison, a study from Germany established an ICER of €19 302 per life-year gained and €30 291 per QALY gained,[142] and a study from Switzerland determined ICERs between €24 792 and €48 369 per life-year gained compared with no screening.[143] In the UK, economic analyses based on the UKLS and the Manchester pilot programme found ICERs of £8466 and £10 069 per QALY gained, respectively.[52,144]

The cost-effectiveness of lung cancer screening also varies depending on the burden of lung cancer in a population. A New Zealand study determined an ICER of $44 000 per QALY gained for biennial low-dose CT screening among individuals aged 55–74 years with at least a 30 pack-year smoking history; however, among Māori, a population group with a higher burden of lung cancer than non-Māori individuals, the ICER was substantially lower at only $26 000 per QALY gained.[145] In Taiwan, a study determined the ICER of

implementing three annual CT screenings relative to annual chest x-rays to be $19 683 per QALY in a population with high-risk smoking history.[146] In countries in which a substantial proportion of lung cancer occurs in people who have never smoked, it will also be important to study the cost-effectiveness of lung cancer screening in those with risk factors other than smoking.

A crucial aspect to consider in cost analyses is overdiagnosis, since treatment of non-progressive or very slow-growing cancers is an important driver of costs with generally no patient benefit but with the potential for harm.[68,138,147] Participant selection criteria, screening intervals (eg, annual *vs* biennial), management of indeterminate lung nodules and incidental findings, and integrated smoking cessation interventions can have a substantial impact on cost-effectiveness. In the future, personalised screening intervals and refined risk stratification of currently indeterminate lung nodules could increase the cost-effectiveness of lung cancer screening.[148,149]

Future directions in lung cancer screening

Personalised screening intervals

Extending the interval between low-dose CT scans for lung cancer screening participants at lower risk of lung cancer could substantially reduce the number of scans performed each year, reduce screening programme costs, and reduce radiation dose to the individual. Conversely, reducing the interval between scans in patients at increased risk could reduce the number of delayed lung cancer diagnoses which confer a worse prognosis.[66,150] The development of strategies to risk-stratify lung cancer screening participants—thereby allowing for personalised screening intervals—could substantially improve the efficiency of lung cancer screening and is an active area of research.

Optimal screening intervals can be informed by patient demographics and other established risk factors such as smoking, emphysema, and history of cancer; information from previous chest CT scans, including the presence of lung nodules and emphysema; and biomarkers.[66,150,151] For example, the LCRAT model was extended to include low-dose CT findings—including CT-detected emphysema and consolidation—to predict the risk of lung cancer at the next annual screen.[152] This approach extended the screening interval for a proportion of lung cancer screening participants on the basis of their estimated risk of lung cancer at the next annual screen, but resulted in an increased incidence of delayed lung cancer diagnoses. A retrospective analysis of NLST data showed that for a risk threshold of less than 0·1% risk of lung cancer at next screen, 15·1% of screen-negative participants would have a longer screen interval, but 0·7% of lung cancers would be diagnosed with a delay.[152] Risk thresholds based on an extended version of the $PLCO_{m2012}$ model ($PLCO_{m2012results}$) were similarly used to identify participants who should continue to undergo annual screening, and participants for whom the screening interval could be safely extended to 2 years.[150] Another study compared five risk models to assign participants to 1-year or 2-year screening intervals.[151] Among the models compared, a polynomial model that incorporated age; smoking history; previous diagnosis of cancer; previous diagnosis of COPD; and nodule size, characteristics, and number had the highest discriminatory ability to assign participants to 1-year or 2-year screening intervals.[151]

External, prospective validation is essential to ensure that risk models can be safely applied in lung cancer screening programmes to stratify participants for personalised screening intervals. The 4-IN THE LUNG RUN (Towards Individually tailored Invitations, Screening Intervals, and Integrated Co-morbidity Reducing Strategies in Lung Cancer Screening) trial is a randomised controlled trial that plans to randomly assign 24 000 participants in the UK, the Netherlands, Germany, Spain, Italy, and France with a normal baseline low-dose CT screen to annual screening or a risk-based screening interval (biennial screening).[18] The need to personalise screening intervals is also a driver of research into artificial intelligence and biomarkers.[19,20,153]

Artificial intelligence

Artificial intelligence, including machine learning and deep learning, is expected to change lung cancer screening. Artificial intelligence could have a role across the entire lung cancer screening workflow, including radiation dose reduction, lung nodule detection, lung nodule characterisation, and personalised screening intervals.[149,154–157] It could also assist in low-dose CT scan interpretation in geographical regions without qualified radiologists. Continued development of artificial intelligence is of particular importance in view of increased workload if lung cancer screening is implemented more broadly, and of the need for standardised image quality and lung nodule evaluation.

New deep learning-based image-reconstruction techniques can reduce image noise,[154] allowing for lower radiation dose and improved image quality.[158] A deep learning image reconstruction technique applied to ultra-low-dose CT (0·07 mSv or 0·14 mSv) resulted in a higher nodule detection rate and improved measurement accuracy compared with ultra-low-dose CT reconstructed using conventional algorithms, suggesting that artificial intelligence could enable the use of ultra-low-dose CT.[158]

Artificial intelligence algorithms have demonstrated high sensitivity (83–97%) and accuracy (82–98%) for lung nodule detection.[159] Deep learning-based algorithms can now outperform radiologists' detection of nodules, in particular for smaller nodules.[160] Novel approaches combining algorithms and employing convolutional networks have reduced the false-positive rate to about one false-positive nodule per scan.[155] Most of the available software solutions require a radiologist to review all nodule candidates identified by the software to determine whether or not they represent true nodules.[161] So far, most

attention has focused on the use of artificial intelligence as a first or second reader to improve sensitivity of lung nodule detection.[155,159,160] Artificial intelligence might also have a role in triaging studies with suspicious or urgent findings and in pre-screening negative scans.[156]

Artificial intelligence tools that express a malignancy probability could help to classify lung nodules as benign or malignant,[157,162–164] and recent algorithms show performance on a par with that of thoracic radiologists.[157,162] Artificial intelligence for lung nodule classification could optimise nodule management by reducing unnecessary work-up of benign nodules, reducing time to diagnosis of malignant nodules, and reducing inter-reader variability. In the future, combining artificial intelligence output with existing guidelines such as Lung-RADS could provide an improved framework for nodule management.[149] Artificial intelligence algorithms can also detect and classify incidental findings on low-dose CT examinations, including coronary artery calcium and emphysema.[165] Artificial intelligence algorithms that use low-dose images and clinical information to estimate lung cancer risk could personalise screening intervals, thereby optimising resource utilisation. A recent example is Sybil, an externally validated deep learning algorithm that predicts future lung cancer risk out to 6 years on the basis of a single low-dose CT without the need for human input or image annotation.[166]

A drawback of many published artificial intelligence algorithms is that they have not been externally validated,[164] and many are not yet available as commercial products for clinical use. An up-to-date overview of CE-marked and US Food and Drug Administration-cleared artificial intelligence software products for lung nodule detection and measurement is now available.[167]

Biomarkers

Blood-based biomarkers might have a role in refining selection criteria for lung cancer screening, aiding the management of indeterminate lung nodules, supporting individualised screening intervals, and helping to predict response to adjuvant therapy. Incorporating biomarkers could be especially important in Asian populations because of the high incidence of lung cancer in people who have never smoked. In a retrospective analysis of samples from a subset of the Multicenter Italian Lung Detection (MILD) trial,[168] a plasma microRNA signature classifier reduced the false-positive rate for non-calcified nodules larger than 5 mm in diameter from 19·4% to 3·7%.[169] The miR test, an miRNA signature for 13 microRNAs, was applied to more than 1000 high-risk participants in the Continuous Observation of Smoking Subjects (COSMOS) study[170] and showed overall accuracy for diagnosis of lung cancer of 75% (95% CI 72–78).[171] The potential for a microRNA signature classifier to safely inform screening intervals following baseline low-dose CT was evaluated in the BioMILD trial.[153] Although the high negative predictive value of low-dose CT limited the added value of blood miRNA results among those with a negative scan, results suggest that among participants with positive scans, the predictive ability of the biomarker could effectively inform decisions regarding biopsy or timing of interval follow-up scans.[153]

The EarlyCDT-Lung test, a measure of autoantibodies to lung cancer-associated antigens, is one of the only biomarkers that has been prospectively evaluated.[172] When applied to 1613 patients deemed to be at high risk for lung cancer, the test showed positive predictive values of 9–16% for a diagnosis within 6 months, depending on whether a six-autoantibody or seven-autoantibody test was used.[173] In a subsequent analysis, the Early Diagnosis of Lung Cancer Scotland (ECLS) trial randomly assigned more than 12 000 high-risk participants to seven-autoantibody EarlyCDT-Lung testing plus low-dose CT if the EarlyCDT-Lung test was positive (only 9·8% of participants) or to standard clinical care and showed, after 2 years, a lower incidence of stage III or IV lung cancer in the intervention group than in the standard clinical care group.[172] When assessed in a cohort of participants from the German Lung Cancer Screening Intervention Trial, the test showed sensitivity of only 13% and specificity of 89–91%, suggesting that it should not replace low-dose CT in high-risk populations.[174]

A proof-of-principle study from the Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) Consortium showed that a panel of four circulating protein biomarkers could be used to identify high-risk individuals for lung cancer screening, demonstrating an AUC of 0·83 compared with 0·73 for a model based on smoking alone.[175] Work from the INTEGRAL Consortium continues to identify and evaluate proteins that might in the future be used to help define lung cancer screening eligibility and differentiate benign versus malignant nodules seen on low-dose CT.[176] The SUMMIT trial aims to assess the performance of a multi-cancer early detection blood test based on high-intensity sequencing of cell-free nucleic acids for lung cancer detection.[19,20]

Other promising biomarkers for early detection of lung cancer include complement fragments, circulating tumour DNA (less well established for lung cancer screening than for advanced disease), DNA methylation, protein profiling and genetic analysis of endobronchial epithelial cells,[177] as well as enzyme-linked immunosorbent assay panels and single nucleotide polymorphisms.[178]

Exhaled breath, including exhaled breath condensate, has also been investigated for lung cancer detection.[179] Exhaled breath condensate includes cells and DNA fragments, whereas volatile organic compounds in exhaled breath can be analysed by gas chromatography or mass spectrometry, nanosensors, and colorimetric sensors.[177]

Implementation considerations

Because of the high resource requirements for lung cancer screening programmes and evolving evidence for screening, relatively few national organised lung

Panel: Goals, challenges, and opportunities for lung cancer screening programmes

Selection criteria

Goals

- Identify individuals at high risk for lung cancer who do not have comorbidities that might preclude them from benefiting from screening

Challenges

- Risk models such as $PLCO_{m2012}$ and LLP_{v3} are more burdensome than categorical criteria and more challenging to implement at a population level using existing health records
- A substantial proportion of patients with lung cancer—particularly in Asian countries—do not have a history of smoking, and categorical selection criteria and risk models developed in high-income countries in Europe and North America could miss a substantial proportion of the population who could benefit from screening

Opportunities

- Further expansion of risk models might better identify individuals who could benefit from screening and increase the efficiency of lung cancer screening
- Further development and implementation of risk models for Asian populations with a high proportion of lung cancer in people who have never smoked
- Validation and integration of biomarkers into risk models
- Development of AI tools for analysis of the baseline CT scan to determine whether screening should continue and optimise screening intervals

Participant recruitment

Goals

- High levels of participation to ensure the greatest number of high-risk individuals benefit from lung cancer screening

Challenges

- Participation in lung cancer screening, both in trial settings and in established programmes, remains low
- Provider barriers include poor knowledge about lung cancer screening, insufficient time to identify patients for screening, concerns about taking responsibility for lung cancer screening without appropriate resources, concerns about the risk of false-positive results, and the absence of clear follow-up pathways for results
- Patient barriers include risk of false positives, distrust of the health-care system, smoking-related stigma, inconvenience, fear of a cancer diagnosis, and worries about financial cost

Opportunities

- Community-based education and awareness programmes for potential participants and primary care providers
- Electronic alerts to remind primary care providers to discuss lung cancer screening
- Readily available decision aids to support shared decision making with participants
- Use of different terminology (ie, lung health checks) might promote greater participation than lung cancer screening

CT image acquisition

Goals

- Efficient acquisition of high-quality images with low radiation dose and minimal variability between facilities
- Integrated smoking cessation interventions

Challenges

- Geographical access to CT facilities for participants in rural and remote communities
- Variability between scanner models and institutions limits development of AI algorithms

Opportunities

- Standardisation of CT acquisition protocols across CT scanners and facilities
- National accreditation for CT facilities and national and international registries for quality assurance and quality improvement
- New CT technologies and post-processing techniques to further reduce radiation dose and increase image quality
- Increasing geographical accessibility to lung cancer screening using mobile CT scanners

CT examination interpretation

Goals

- Efficient detection of malignant lung nodules and other findings of clinical significance
- Clear recommendations for management of findings with minimal variability between readers

Challenges

- Large volume of studies results in a high workload for readers and high costs to the health-care system
- Variation in interpretation between readers

Opportunities

- Dedicated pool of readers with minimum training requirements
- Standardised reports that direct appropriate follow-up
- AI for lung nodule detection and lung nodule risk stratification
- AI for standardisation of coronary artery calcium scoring and assessment of emphysema

Management and follow-up

Goals

- Prompt and safe investigations to enable treatment for cancers that are likely to reduce life expectancy or reassurance and return to the screening programme for those people with benign or indolent disease
- Prompt and safe management of incidental findings that are likely to reduce life expectancy or reassurance for those findings that are not clinically significant

Challenges

- Absence of clear follow-up pathways for positive findings
- Burden on the health system related to investigations of indeterminate lung nodules and incidental findings

(Panel continues on next page)

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- Pressure on the thoracic surgical workforce, with projected increase in cases referred for curative surgery

Opportunities

- Establishment of clear guidelines and protocols regarding lung nodule management and management of incidental findings to reduce harms and costs
- Establishment of dedicated lung nodule clinics and dedicated lung cancer screening staff to help manage imaging findings
- Automatic electronic medical record system reminders for recommended follow-up
- Validation of AI and biomarkers to assist in risk stratification of indeterminate lung nodules

Communication of results

Goals

- Timely and consistent communication of results to participants and health-care providers to support shared decision making and patient empowerment

Challenges

- Disclosure of results by letter might lead to participant distress
- Conversations between participants and health-care staff can be time consuming

Opportunities

- Standardised reports distributed to participants in simple language to empower their decisions
- Lung cancer screening coordinators to support communication of results to participants and coordinate appropriate follow-up

AI=artificial intelligence. LLP_{v2}=Liverpool Lung Project risk prediction model version 2. $PLCO_{m2012}$= Prostate, Lung, Colorectal and Ovarian risk prediction model version m2012.

cancer screening programmes have been implemented. Countries with national or nationally funded screening programmes—or countries in which lung cancer screening is a nationally covered insurance benefit—include the USA, Poland, Croatia, and South Korea.[35,45,180] Many other countries have launched pilot projects or lung cancer screening programmes on a smaller scale, such as Canada and many European countries.[94,181,182] In 2022, the UK National Screening Committee recommended that the four UK nations move towards implementation of targeted lung cancer screening for people aged 55–74 years at high risk of lung cancer, together with integrated smoking cessation.[183] Also in 2022, the Australian Government Medical Services Advisory Committee recommended the introduction of a National Lung Cancer Screening Program for individuals aged 50–70 years with a high risk of lung cancer due to cigarette smoking.[33]

Lung cancer screening implementation carries many challenges even in well-resourced settings, needing a large and dedicated team, multidisciplinary expertise, and strong clinical and administrative leadership.[184] Implementation of screening can challenge health systems so that even in a single system, important variations can affect screening uptake by eligible individuals[185] and adherence to follow-up recommendations.[186] Addressing common challenges across the screening continuum—ranging from participant selection, recruitment methods, image acquisition and interpretation, nodule management and referral, and communication of results—is essential for lung cancer screening programmes to maximise benefit and minimise harm (panel).

Cancer screening relies on high levels of participation to realise the full benefits of any programme, yet lung cancer screening participation, both in pilot settings and in established programmes, remains low. In the USA, one of the first nations to introduce lung cancer screening, with the United States Preventive Services Task Force recommending lung cancer screening with low-dose CT in 2013, fewer than 4% of eligible participants have had screening based on 2016 national Lung Cancer Screening Registry data.[187] Survey data from the Behavioral Risk Factor Surveillance System showed that participation rates seem to be climbing, with lung cancer screening participation of just over 14% of USPSTF-eligible candidates in 2017 and more than 17% in 2018.[188,189] In the UK, lung cancer screening trial participation falls short of that in other cancer screening programmes. In a trial specifically designed to maximise participation in socioeconomically deprived groups in the UK, the Lung Screen Uptake Trial showed an overall 53% uptake in attendance at a lung health check, with 38% of the total participants undergoing low-dose CT.[16] This figure is lower than national participation rates for cervical (65%), breast (70%), and colorectal (60%) cancer screening.[190] Factors that might contribute to low participation rates include poor awareness of lung cancer screening,[191] concerns about the risk of false positives,[191,192] distrust of the health-care system,[193] smoking-related stigma,[193] inconvenience,[191,193] fear of a cancer diagnosis, and worries about financial cost.[191]

Providers, in particular primary care providers who have front-line roles in identifying lung cancer screening participants, can also face barriers that hinder recruitment, including inadequate time or staffing to discuss lung cancer screening in detail with patients,[192,194] little or no knowledge about screening,[195] concern about health system burden and costs,[191,196] the risk of

false-positive results, and lack of clear management pathways for screen-detected findings.[191]

Screening programmes might consider various strategies to overcome these barriers, including education and outreach initiatives, automatic electronic medical record system reminders, unambiguous referral guidelines and management protocols for screen-detected findings, and dedicated lung nodule clinics.[192,194,196,197] Pre-invitation letters, scheduled appointments, and reminder letters have been shown to increase screening participation.[190] Lung cancer screening programmes that use risk calculators, more burdensome than categorical criteria, should develop tools to support primary care providers in identifying eligible individuals, as well as decision aids to support discussions with potential participants.[198] Personalised discussions about lung cancer screening between patients and clinicians might help to overcome fear and resistance, but these require time—a factor to consider in developing lung cancer screening consultation processes.[191]

Lung cancer screening programmes must focus on health equity. Disparities in screening might result from dissimilarities in racial and ethnic background, access to smoking cessation interventions, use of preventive services, and geographical barriers.[69] Although expansion of the USPSTF criteria in the USA was aimed at overcoming the risk of missing high-risk candidates who did not meet earlier benchmarks and who have poorer lung cancer outcomes with a lighter smoking history, racial and ethnic minority groups continue to be less likely to be eligible for lung cancer screening than non-Hispanic White individuals, potentially perpetuating lung cancer disparities.[199,200] Rural residents might experience poorer lung cancer outcomes than people living in urban areas, and geographical barriers to lung cancer screening also exist.[201] An Australian survey of rural and remote Indigenous community members and health-care workers reported several barriers to lung cancer care, including absence or paucity of public transport, inadequate communication, and lack of coordination between health services.[202] Identifying culturally safe approaches will be critical to ensuring equitable access to lung cancer screening. Mobile CT scanners could help to overcome some of the geographical barriers to access lung cancer screening. A study that compared lung cancer screening using hospital-based scanners with mobile scanners[27] showed that 23% of second-round attendees who attended the mobile service indicated they would be less likely to participate in lung screening if it was hospital-based.[203] Offering ride-sharing services at no charge to participants who do not have a reliable means of transportation could also reduce barriers for patients accessing screening.[204]

The feasibility of lung cancer screening in resource-poor countries requires careful consideration, especially because 80% of the world's population who smoke live in low-income and middle-income countries.[205,206] Limitations in infrastructure, human resources, the capacity to effectively manage screen-detected findings, and financial resources are some of the challenges faced in the implementation of lung cancer screening in low-income and middle-income countries.[207] Despite these challenges, a large prospective cohort study in China that was part of the National Lung Cancer Screening programme suggested that implementing one-off low-dose CT screening in resource-poor countries is feasible, potentially providing an example for other countries regarding the large-scale implementation of lung cancer screening.[21] Strategies that could be used in the future to lower the cost of lung cancer screening programmes in low-income and middle-income countries include use of artificial intelligence for image interpretation, optimisation of scan intervals, and a primary focus on lung cancer prevention through tobacco control, smoking cessation, and reducing air pollution.[205]

Conclusions

Randomised controlled trials have shown that low-dose CT for lung cancer screening can help to reduce lung cancer mortality, and the development of a broad evidence base during the past three decades has supported the adoption of lung cancer screening across many health systems with disparate characteristics. Further research into personalised screening intervals, integrated assessment of COPD and cardiovascular risk, artificial intelligence, and biomarkers are key opportunities to increase the efficiency of lung cancer screening. Geographical differences in the incidence of lung cancer, such as the large proportion of patients with lung cancer among people in Asian countries who have never smoked, will require special attention to refine selection criteria and risk models to effectively engage high-risk individuals and promote health equity. Continued research and widespread adoption of evidence-based strategies could allow lung cancer screening to reach greater numbers of people and improve population health worldwide.

Contributors

All authors contributed to developing the outline for the Review, conducting the literature search, assessing and interpreting available evidence, and writing the Review. All authors approved the final version of the manuscript.

Declaration of interests

ES reports advisory board payment or honoraria from Merck Sharp & Dohme in which she provides expert advice on an ad-hoc basis and speaker honoraria from AstraZeneca. DRB reports speaker honoraria from MSD, Bristol Myers Squibb, AstraZeneca, and Roche. RV reports research grants from Siemens Healthineers, Dutch Heart Foundation, Dutch Cancer Foundation, and the Netherlands Organisation for Health Research and Development, and speaker honoraria from Siemens Healthineers and Bayer. FJF reports research grants from the William M Wood Foundation and the American Roentgen Ray Society, and in-kind research support from Boston Scientific. SJA and PL declare no competing interests.

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