Lung cancer LDCT screening and mortality reduction — evidence, pitfalls and future perspectives— evidence, pitfalls and future perspectives

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Abstract | In the past decade, the introduction of molecularly targeted agents and immune-checkpoint inhibitors has led to improved survival outcomes for patients with advanced-stage lung cancer; however, this disease remains the leading cause of cancer-related mortality worldwide. Two large randomized controlled trials of low-dose computed tomography (LDCT)-based lung cancer screening in high-risk populations, NLST and NELSON, have provided evidence of a statistically significant mortality benefit in patients.

LDCT-based screening programmes for individuals at a high risk of lung cancer have already been implemented in the USA, and implementation programmes are currently underway in the UK following the success of the UKLS trial, which included;

the Liverpool Health Lung Project, the Lung Screen Uptake Trial, the West London Lung Cancer Screening pilot and the Yorkshire Lung Screening trial.

In this Review, we focus on the current evidence on LDCT-based lung cancer screening and discuss clinical developments in high-risk populations worldwide; we also address aspects such as cost-effectiveness. We present a framework to define the scope of future implementation research on lung cancer screening programmes referred to as Screening Planning and Implementation RAtionale for Lung cancer (SPIRAL).

[H1] Introduction

Lung cancer is currently both the most commonly diagnosed cancer (accounting for 11.6% of all cancer diagnoses) and the leading cause of cancer-related mortality (18.4% of overall cancer mortality) in both men and women worldwide[1]. In the past decade, the introduction of molecularly targeted agents and immune-checkpoint inhibitors into the therapeutic armamentarium for patients with stage IV (advanced stage) lung cancer has led to improved survival outcomes[2]. These therapeutic approaches, however, are beneficial only for restricted subsets of patients and, thus, the majority of them die within 5 years of lung cancer diagnosis[1]. However, Stage 1A disease patients have > 75% chance of survival over 5 years[3]. To date, the main strategy shown to substantially reduce lung cancer mortality over a longer time period is predicated on early detection using low-dose computed tomography (LDCT)-based screening in asymptomatic individuals[4–7]. In settings in which lung cancer screening programmes have been implemented, annually ~1–3% of participants are diagnosed with lung cancer, 50–70% of them with stage I (early stage) disease[7–13]. These patients usually undergo surgery with curative intent, with other available therapeutic options being stereotactic radiotherapy,

brachytherapy and percutaneous tumour ablation. Lung cancer is a tobacco-related disease: in high-income countries, ~10–20% of current and former heavy-smokers will be diagnosed with lung cancer during their lifetime compared with 1–2% of never-smokers[14,15]. Thus, individuals with a history of smoking are likely to derive the greatest benefit from screening.

In this Review, we discuss the current evidence supporting the effectiveness of implementing national lung cancer screening programmes and also how such programmes should be developed in the future. We focus on aspects such as identification of the target population, participant recruitment and compliance, screening frequency**,** integrated smoking cessation interventions, cost-effectiveness and sex differences. We also present an overview of current lung cancer screening programmes worldwide and discuss future opportunities to leverage artificial intelligence (AI) in LDCT-based lung cancer screening. All of these areas should be considered in the scope of future implementation research programmes on lung cancer screening, in a framework we refer to as Screening Planning and Implementation RAtionale for Lung cancer (SPIRAL) (FIG. 1).

[H1] Identification of a high-risk population

To minimize potential harms associated with cancer screening (such as exposure to radiation) and maximize its effectiveness, screening programmes should be limited to individuals who are at high risk of a particular cancer within the general population[16]. Typically, screening programmes are focused on a prespecified subset of individuals within the general population on the basis of either age (for example, in colorectal cancer screening) or a combination of age and sex (such as in

breast and cervical cancer screening). For lung cancer screening, an improved approach has been implemented in the UK through several lung cancer CT screening implementation studies: the Liverpool Healthy Lung project[17], Manchester Health lung Check[18], West London Cancer Screening pilot[19] and Yorkshire Lung Screening trial[20]. Besides age (>60 years), smoking status has been shown to have the greatest influence on the probability of developing lung cancer (ie odds ratio for smoking duration 1-19 years compared >60years 2.17 (1.21–3.85) vs. 15.25 (5.71–40.65 [21]. However, several other factors also contribute to this risk, including family history of lung cancer (especially for individuals aged <60 years ie odds ratio for early onset compared to late onset ; 2.02 (1.18–3.45); 1.18 (0.79–1.76[21])) and individual history of other respiratory diseases, other malignancies and exposure to asbestos. Other risk factors have been reported in the literature, including exposure to radon and a number of other carcinogens (such as diesel exhaust fumes), but to date they have not been included in any of the validated risk models.

The use of prediction models integrating several risk factors in lung cancer-screening research has gained credence over the past 10 years. Indeed, the use of validated risk models is integral to all current screening and early detection programmes in Europe. Several multivariable risk prediction models have been published and reviewed recently [22]; however, only two — $PLCO_{M2012}$[23] and LLP_{v2}[24] — have thus far been used to guide the selection of participants in lung cancer screening clinical trials and projects. In the US National Lung Screening Trial (NLST), current and former heavy-smokers (current smokers; 30 or more pack-years of cigarette smoking history; former smokers: quit smoking within the previous 15 years).

aged 55–74 years were randomly allocated to undergo three annual rounds of screening with chest LDCT or single-view chest radiography[4]. The NLST dataset has been analysed using several risk-prediction models, leading to the conclusion that the NLST selection criteria and the United States Preventive Services Taskforce (USPSTF) criteria recommendations for lung cancer screening could have been greatly improved if a risk model incorporating variables beyond age and smoking history had been implemented[25–27].

Currently, $LLPv_2$ is the only risk model that has been used to select participants in a randomized controlled trial (RCT) of lung cancer screening: in the UK lung cancer screening (UKLS) trial[28], a 5-year lung cancer risk ≥5% according to LLP_{v2} was used as an inclusion criterium, together with an age of 50–75 years. Participants in this trial underwent LDCT-based screening or no screening. The percentage of participants with lung cancer identified in the LDCT arm at baseline (1.7%) was higher in UKLS than in the NLST or NELSON (1.03% and 0.9%, respectively)[28]. Of note, NELSON involved current and former heavy-smokers (≥30 pack years) aged 55–75 years who were randomly allocated to several rounds of chest LDCT-based screening or no screening. The LLP_{v2}-based criteria used in the UKLS trial were subsequently adopted to select participants in the Liverpool Healthy Lung Programme[17]. The UK is currently leading the way in Europe in terms of implementing lung cancer early detection with LDCT-based screening, with major programmes ongoing in the Liverpool[17], Manchester[18], Yorkshire[20] and London[19,29] regions. Moreover, in 2019, NHS England provided major investment to introducing a national programme in ten new regions in 2019[30]. These new programmes will involve a combination of both the $PLCO_{M2012}$ and LLP_{v2} risk models

to recruit participants, thus demonstrating interest in targeted recruitment approaches.

In one of the most comprehensive analyses, nine different risk models were used to analyse data from the Prostate, Lung, Colon, and Ovarian cancer screening (PLCO) trial and NLST datasets[22]. The selected sophisticated models incorporated well-documented risk variables (such as family history of lung cancer, previous malignancy, previous respiratory disease and exposure to asbestos). However, not all risk factors were considered in these comparisons, which were only based on age, sex and tobacco-related factors, thus underestimating the lung-cancer risk of never-smokers. The $PLCO_{M2012}$ model had the best predictive performance in this analysis, with an area under the curve (AUC) >0.77. Several studies have also shown the cost-effectiveness of screening in high-risk populations, leading to the conclusion that improved risk-prediction models would further reduce costs per life years (LYs) saved [22,31]. The cost-effectiveness analysis only revealed a modest gain of additional LYs. In addition, use of lung cancer prediction models increased the risk of overdiagnosis owing to preferential selection of older individuals; thus the researchers concluded that the future development of risk-based lung cancer screening needs to incorporate life expectancy[31].

Using risk models in national screening programmes has potential limitations that must be acknowledged. In particular, information on risk variables has to be either available in primary health-care records or obtained directly from the patient. Collection of these data in the UK implementation studies has involved a two-step process, whereby all patients with a smoking history in the primary care notes and/or electronic health records were invited and then, a structured questionnaire was provided to them at the time they were consented into the studies. However, smoking

history is not always recorded in primary care notes and thus might be challenging in other countries and not a feasible approach. The advent of social media and the use of clinical apps might provide solutions for obtaining information on risk variables directly from patients, but these approaches remain in early stages of development.[32]

Currently, none of the validated prediction models to identify individuals with a high risk of lung cancer have incorporated biomarkers or susceptibility genes, even though major efforts have been undertaken in this regard[33]. Integral, a major lung cancer programme from the NIH[34], is currently focused on this topic and has generated some early encouraging data on the integration of genetic susceptibility pathways[35–37] and circulating biomarkers[38] in risk-prediction models. Indeed, the next stage in the development of risk-prediction models will have to move beyond epidemiological and clinical data to also include validated biomarkers. This active area of research will require access to current CT-screening biobanks as well as the development of high-quality prospective biobanks embedded in future screening programmes together with radiomics data (volume and density growth characteristics). Future molecular tests not only need to be validated, but also cost-effective, possibly using nanotechnology-based approaches [39].

[H1] Recruitment and adherence issues

The real-world experience in the USA, where only a fraction (<5%) of individuals at high risk of lung cancer are screened, demonstrates the difficulties in effective recruitment of participants in national screening programmes, even when they are endorsed by most major medical societies[40]. The challenges of recruitment and

screening adherence differ between regions because they depend on the nature of the health-care system as well as on the public and physician opinions on screening — clearly, a unique approach has to be chosen for each country. Nevertheless, two principles should be common to all approaches to recruitment: screening should only be implemented for high-risk individuals; and appropriate presentation of potential benefits and risks is crucial[41]. Experience from the UKLS trial has revealed that, especially in the first stage of recruitment, current smokers and individuals from lower socioeconomic groups are least inclined to participate[42,43]. For current smokers, emotional barriers seem to represent a central obstacle to screening participation[42]. More than ever, primary care physicians could be the focal point in ensuring screening uptake by individuals who are mostly likely benefit[40]. Other major contributors to the low uptake of screening might be the false-positive rate (when a nonmalignant nodule is detected; 24% [16])
that was reported in the NLST trial[4] and also the perceptions of some patients and carers[44]. In the NELSON trial, however, with results published 9 years after those from the NLST and incorporating optimized nodule-management protocols and risk-stratification algorithms, the false-positive rate was only 1.2% and the referral rate only 2.1%[10]. Of note, the definition of positive screen result differed between the NLST and NELSON study: in the NLST the two possible outcomes of a chest LDCT or radiography were ‘negative’ and ‘positive’, but in NELSON ‘indeterminate’ was introduced as a new classification[45,46]. Only when indeterminate nodules were found to have grown at a short-term follow-up LDCT scan was the indeterminate screen result reclassified as positive.

Eventually, the successful recruitment of individuals at high risk of lung cancer will depend on the combined efforts of primary-care physicians and specialists. In

order to ease the pressure on the former, the responsibility for determining an individual's eligibility has to be considered as a multidisciplinary activity and thus, discussions around shared decision-making, counselling for smoking cessation and potential treatment options should be combined across clinical specialties.

Challenges in the recruitment of high risk and hard to reach individuals remain one of the major barriers to the implementation of lung cancer screening programmes. Even among the most efficient centres in terms of recruitment in ongoing UK implementation projects, few have a participation rate >50%[17–19].

[H1] Radiological evidence

The aim of lung cancer screening is to enable early detection of malignant nodules in order to eventually reduce cancer-related mortality. Before the 2010s, the technical performance of chest radiography, alone or in combination with sputum cytology, was evaluated in population-based lung cancer screening programmes[41,47]. However, these studies did not show reductions in lung cancer mortality and the screening method was proven not to be sensitive enough[47–49]. In the 2000s, the introduction of LDCT renewed interest in assessing the performance of imaging-based lung cancer screening approaches[47]. A chest LDCT entails a radiation dose of ~1.5 mSv, which is 15-fold higher than the dose delivered to obtain a conventional chest X-ray but <25% of that delivered with conventional chest CT[50].

While other diagnostic methods, such as MRI or genetic testing, have been explored in population lung cancer screening, results from RCTs that would support their use in current clinical practice are not available[47,51,52]. Currently, LDCT-based lung cancer screening is the only screening approach that has resulted in a statistically significant reduction of lung cancer-related mortality in two independent sufficiently

powered RCTs (FIG. 2)[4,10]. In 2011, researchers from the NLST reported a 20.0% reduction in lung cancer-related mortality after a median follow-up of 6.5 years (P = 0.004) in patients undergoing three annual LDCT-based screenings compared with those undergoing chest radiography screening with the same frequency[4]. The overall mortality reduction in the LDCT group was 6.7% (P = 0.02). In 2020, results from the NELSON trial showed a cumulative rate ratio (RR) for death from lung cancer in men of 0.76 (95% CI 0.61–0.94) in the screening arm relative to the control arm at 10 years[10]. The cumulative RR for all cause mortality was 1.01 (95% CI 0.92–1.11). Nevertheless, implementation of LDCT in screening programmes is still ongoing in the USA and anticipated in Europe in the next decade[41,47,53,54].

[H2] Nodule prevalence and risk stratification

Effective risk-stratification and management of detected lung nodules is crucial for the success of any lung cancer screening programme. Baseline nodules with an unknown developmental timeframe need to be distinguished from new nodules (after baseline) that have developed within a known timeframe[55]. Depending on the detection limit, 22–51% of participants in screening RCTs have a lung nodule detected at baseline[56–65]. Furthermore, available data from the Early Lung Cancer Action Project (ELCAP)[66], International (I)-ELCAP[63], Pittsburgh Lung Screening Study[56], Mayo trial[67], NLST[68] and NELSON trial[55] suggest that, annually 3–13% of participants develop a new nodule after any baseline screening, negative or positive. Importantly, the majority of lung nodules detected, either at baseline or thereafter, are small. Data from lung cancer screening trials with none or a very low detection limit (>3 mm or >15 mm^3; Mayo trial[67], ELCAP[66], I-ELCAP[63], NELSON[55]) suggest that >50% of the detectable lung nodules have a volume <50 mm^3 or a maximum diameter <5 mm[55,57,58,60,61,66,67,69]. Similarly, the NLST (with a detection limit of 4 mm

for the longest diameter) revealed a baseline nodule prevalence of 51% for nodules of 4–6 mm. The detection of multiple nodules is common in screening practice: ~50% of participants have more than one nodule at baseline and >20% of those who develop new nodules have multiple nodules; each nodule requires a separate risk assessment[70,71].

[H2] Nodule size assessment

An accurate and reproducible assessment of nodule size is central to ensuring appropriate nodule management. The assessment of nodule size has been routinely based on the manual measurement of the longest diameter[72,73]. Nevertheless, this approach was shown to be unreliable when compared with subsequent methods, such as volumetry, because pulmonary nodules are seldom perfectly geometrically shaped[74,75]. Several European lung cancer screening trials (FIG. 2) have incorporated volumetry involving semi-automated volume estimation after 3D reconstruction of thin CT slices of nodules[6,10,51,55,61]. This approach was advocated in the European Statement on Lung cancer Screening (EUPS)[16] and was subsequently implemented in clinical practice guidelines from the British Thoracic Society (BTS), suggesting that whenever available, volumetry should be preferred to diameter measurements[47,72,76,77]. Moreover, in the 2019 Lung Imaging Reporting and Data System (Lung-RADS) screening guidelines, volume standards have been added as a more reproducible alternative to manual linear measurements whenever appropriate software is available[47,53].

[H2] Nodule growth

With the use of appropriate size cut-offs, most nodules detected during lung cancer screening can be classified as low-risk or intermediate-risk nodules and decisions can be made on additional follow-up screens (regular (1 year) or short-term (3 months) according to the EUPS[16]). At follow-up screens, risk stratification should be based on nodule growth[47,72,76,77]. Again, considering that most nodules detected in lung cancer screening are very small, tumour growth assessment based on 2D diameter evaluation has been considered unreliable compared with volumetry[77]. For example, in the Lung-RADS screening guidelines, growth has been defined as an increase of >1.5 mm in diameter or >2 mm^3 in volume[53]. In a spherical nodule with a diameter of 5 mm (and thus, a volume of ~65 mm^3), a diameter increase to 6.5 mm would result in a more than doubled volume (144 mm^3) whereas a volume increase to 67 mm^3 corresponds to a diameter increase to only 5.04 mm. An analysis of 2,240 intermediate-size nodules (defined as 50–500 mm^3 in volume or ~4.5–10 mm in longest diameter), revealed a median intranodular diameter variation of 2.8 mm, above the 1.5 mm growth threshold, when volume was estimated on the basis of the maximum versus the minimum diameter[75]. Even when nodule diameter was measured semi-automatically, the intranodular variation was ≥2 mm in 85% of nodules[75,77,78]. Importantly, volume measurements have a significantly worse performance in areas with ground glass opacity and in the measurement of part-solid nodules[79]. In Asian populations, in which such nodules are more common[80], volume measurements alone might therefore not be the best option in nodule management, but a combination of the measurement of volume, mass and diameter of these subsolid nodules. Another advantage of volumetry is that it enables calculation of the volume-doubling time (VDT), a widely used surrogate for growth speed[47], as opposed to considering a fixed size increase, which translates into different growth

speeds at different nodule sizes. Even compared with software-guided and optimized diameter measurements, a protocol based on semi-automated nodule volume and VDT measurements yielded the highest specificity (94.9% versus 90.0% with the diameter-based protocol) and positive predictive value (14.4% versus 7.9% with the diameter-based protocol) with similar negative predictive value (99.9% in both protocols) in an analysis of data from the NELSON trial[77,81].

[H2] Nodule subtypes

Radiological detection enables the classification of pulmonary nodules into non-calcified pulmonary nodules, which comprise solid and subsolid nodules, the latter including ground-glass (non-solid) nodules and part-solid nodules, and calcified nodules. From the perspective of lung cancer screening, this distinction is relevant for two reasons. Firstly, both at baseline screening and in subsequent rounds of screening, (new) subsolid nodules are considerably less prevalent than (new) solid nodules, and overall <10% of lung cancer screening participants present with non-solid nodules[47,82–84]. Secondly, compared with solid nodules, non-solid nodules (including premalignancies) are associated with an equivalent or a higher prevalence of lung cancer, but their indolent nature (they are nearly always stage I cancers or in the pre-stages of lung cancer) has been shown both in prospective studies and RCTs[82,83,85–89]. Data from the NELSON trial and EUPS have formed the basis to develop risk-stratification protocols for different LDCT screen-detected nodules[47] (FIG. 3).

[H2] Overdiagnosis and false positives

The identification of clinically significant lung cancer while preventing overdiagnosis and false-positive results is a central challenge in LDCT-based lung cancer screening. In this regard, clinical decision-making upon detection of subsolid nodules is particularly challenging because they are more often malignant than solid nodules but have a slower growth rate[80]. Therefore, continuous benchmarking of risk-stratification algorithms is essential. For example, a comparison of the screening results from NELSON (using a volume-based protocol) and the NLST (using a diameter-based protocol) showed substantial differences in false-positive baseline screening results, with positive-test rates of 2.1% versus 24%, positive predictive values of 43.5% versus 3.8% and false-positive rates of 1.4% versus 23.3%.

[H1] Nodule-based risk-prediction models

The potential of integrating nodule data from LDCT scans with the patient's clinical and epidemiological information has enabled the development of nodule-based lung-cancer risk models. In certain instances, these models have been used in clinical practice not only to manage the radiological diagnostic follow-up but also to calculate the most appropriate time for a follow-up scan.

In 2013, researchers from the Pan-Canadian Early Detection of Lung Cancer Study (PanCan) published several nodule-based risk-prediction models[90], now referred to as the Brock parsimonious model (PanCan-1) and the comprehensive model (PanCan-2).These models were developed using data from 1,871 participants in PanCan and validated using a dataset comprising 1,090 individuals involved in chemoprevention trials from the British Columbia Cancer Agency. These two high-risk screening cohorts had been followed up for a minimum of 2 years to determine the probability of pulmonary nodules detected in LDCT screens being cancerous. A

cancer diagnosis was associated with female sex ($P \leq 0.02$), larger size of the nodule ($P < 0.001$), location of the nodule in the upper lung ($P \leq 0.02$) and nodule spiculation ($P \leq 0.02$). These researchers also developed so-called 'full models', which additionally included older age, a family history of lung cancer, emphysema, lower nodule count and part-solid nodules as compared with solid nodules. These models had very good predictive accuracy, with AUCs >0.94 in the external validation cohort, and thus became the management tool recommended by EUPS and BTS[16,76]. In 2019, PanCan included nodule volume in these models[91]. Both the diameter-based and volume-based models showed very good overall predictive performance in the test and validation datasets, with accuracy similar to that of the previously validated PanCan models: the computer-aided detection (CAD)-assessed mean diameter and volume models both had median AUCs of 0.947 in the PanCan data and of 0.810 and 0.821, respectively, for the NLST dataset[91].

The UKLS dataset has also been used to develop a parsimonious model to estimate the probability of malignancy in lung nodules detected at baseline, 3-month and 12-month repeat screens[92]. The covariates found to enable prediction of lung cancer included female sex, asthma, bronchitis, asbestos exposure, a history of cancer, a family history of early and late onset of lung cancer, smoking duration, lung forced vital capacity, nodule type (pure ground-glass and part-solid) and larger volume (measured by semi-automated volumetry). The final model incorporating all predictors had excellent discriminatory value (with an AUC of 0.885). Internal validation suggested that the model would discriminate well when applied to new data in the future (with an AUC of 0.882) and had good calibration when used with 'bootstrapping' optimization techniques.

A number of groups have attempted to develop other nodule-based risk-prediction models. The Pittsburgh Lung Screening Study cohort constitutes one such approach using probabilistic graphical models to integrate demographics, clinical data and LDCT scan-related features[93]. The investigators noted that the number of nodules and blood vessels as well as the number of years since the individual quit smoking were sufficient to discriminate malignant from benign nodules, with statistically significant coefficients (P <0.05). The incorporation of LDCT scan-related features greatly enhanced the predictive accuracy of this model, improving cancer detection over existing methods, in particular, the Brock parsimonious model (P <0.001). The most notable observation of this study is that the incorporation of information on the number of surrounding vessels significantly improves on the predictive efficiency of previous models[93].

In the German Lung cancer Screening Intervention (LUSI) trial[6], 4,052 long-term smokers aged 50–69 years were randomly allocated to undergo five annual rounds of LDCT-based screening or no screening. Data from this trial were used with the aim of validating several nodule-based risk models, such as the PanCan[91], Mayo Clinic[94], Peking[95] and UKLS models[92] using sophisticated statistical tools[96]. PanCan-1b was found to be the model with the most predictive value in this validation exercise (AUC 0.93) and the UKLS model was considered the least optimal, (UKLS: AUC, 0.58) although the study design did not take into account that some of the UKLS model parameters were not available in the original LUSI dataset, such as family history and exposure to asbestos. By leaving these two variables out and using the other coefficients in the model unchanged, will most likely give biased

estimates. The editorial associated with this publication outlined the pro's and con's of attempting validation of these risk models[96,97].

This study exemplifies the importance of including parameters with a low risk of inter-reader variability in risk models. The inclusion of parameters with a high risk of inter-reader variability, such as diagnosis of bronchitis or discrimination between part-solid and non-solid lung nodules, might strongly reduce the performance of these models for predicting outcomes in cohorts others than those with which they were developed[97]. Of note, all the models discussed herein have reduced performance when used on nodules newly detected after baseline, confirming the need for separate management protocols for these nodules.

[H1] Screening frequency

In LDCT-based lung cancer screening, the duration of the interval between two regular screening rounds (referred to as screening interval) is a crucial determinant of the benefit:harm ratio. By prolonging this interval, cumulative radiation and diagnostic costs decrease, but the probability of a cancer diagnosis outside of the screening programme (so-called 'interval cancers') and/or that of detecting late-stage lung cancer increase. In the USA, lung cancer screening is currently performed through annual LDCTs in high-risk patients, on the basis of the USPSTF recommendations, which in turn are based on the NLST criteria[98]. All countries recommend an annual screening interval; however, the outcomes of the NELSON study suggests that a sex-specific interval could be applied in the future, because nodules tend to have a slower growth rate in women than in men[10].

With the increasing interest in patient-tailored medicine, the question has arisen of whether decisions regarding future screening rounds should be made on the basis of the baseline screening result, enabling the identification of subgroups of patients with lower lung cancer risk who might benefit from a biennial screening interval. To date, evidence from three screening trials (the NLST, Multicentric Italian Lung Detection (MILD) trial and NELSON) contribute to this debate.

Patz et al.[99] retrospectively evaluated the value of annual follow-up LDCT after a negative baseline screening result among participants in the NLST. Among 19,066 NLST participants with a negative baseline result, 441 (2%) were eventually diagnosed with lung cancer. Lung cancer was diagnosed within 2 years after the baseline scan in 92 individuals (0.48%, with 30 interval cancers and 62 screen-detected cancers), 52% with stage I–II cancers. An additional 118 participants had lung cancer diagnosed ≤1 year after the third screening (and thus, 2–3 years after the baseline scan), with 60% having stage I–II cancers. Owing to the very low incidence of lung cancer in the first annual screening round after baseline in participants with a negative baseline LDCT scan, Patz et al.[99] concluded that annual screening might be superfluous in these situations.

In the MILD trial, participants with a high risk of lung cancer (49–75 years of age, who smoked ≥20 pack-years, and were current smokers or quit <10 years before recruitment) were randomly assigned to undergo annual screening (*n* = 1,190), biennial screening (*n* = 1,186), both for a median follow-up of 6 years, or no screening (control group *n* = 1,723). Ten years after the baseline scan, LDCT-based screening (annual and biennial combined) was associated with a significant 39% reduction in lung cancer-related mortality (HR 0.61, 95% CI 0.39–0.95; *P* = 0.017), as well as a nonsignificant 20% decrease in all-cause mortality (HR 0.80,

95% CI 0.62–1.03; *P* = 0.069)[7]. In an additional analysis of the results of MILD, Pastorino et al.[100] showed that lung cancer-related mortality (HR 1.10, 95% CI 0.59–2.05) and overall mortality (HR 0.80, 95% CI 0.57–1.12) at 10 years after baseline screening were similar for participants in the biennial and annual LDCT arms. In this trial, the biennial screening protocol enabled avoidance of up to 44% of follow-up LDCT scans, without an increase in the occurrence of stage II–IV or interval lung cancers. Although the sample size of the MILD trial was underpowered, these results suggest that individuals with a negative baseline result might benefit from undergoing biennial instead of annual screening.

Another approach to addressing whether the screening interval should be considered on an individual basis has been proposed on the basis of a logistic regression model of lung cancer risk at the second annual screen or in the following year. This model, which was only tested retrospectively, included participants' characteristics and radiological observations, such as nodule characteristics at the first screen, using NLST data[101]. For different risk thresholds, Schreuder et al.[101] projected that 2,558 (10.4%), 7,544 (30.7%), 10,947 (44.6%), 16,710 (68.1%) and 20,023 (81.6%) of 24,368 second screens could have been omitted, at the cost of delaying the diagnosis of 0 (0.0%), 8 (4.6%), 17 (9.8%), 44 (25.3%) and 70 (40.2%) of 174 lung cancers, respectively, thus concluding that the screening interval could be extended for certain participants.

In NELSON, the effect of prolonged screening intervals was studied by incorporating different intervals between each repeat round of screening. Participants randomly allocated to the LDCT arm were screened at baseline (year 1) and then in years 2, 4 and 6.5; resulting in one annual screening round, one biennial screening round and one 2.5-year screening round, respectively. The probability of lung cancer

2 years after the baseline scan was determined. Participants with a negative baseline CT, with a newly proposed cut-off volume for the largest nodule <100 mm^3, had a similar very low risk of being diagnosed with lung cancer within 2 years as participants without any baseline nodule (0.6% versus 0.4%, respectively). For participants without any baseline nodule, the 2-year probability of lung cancer was significantly lower than that of participants with intermediate risk nodules (100–300 mm^3; 2.4% probability) or high-risk nodules (>300 mm^3; 16.9%) at baseline, again suggesting that an annual LDCT after a negative baseline CT might not be necessary for some patients. In the NELSON study, the number of interval cancers and stage II–IV lung cancer detected after a screening interval of 2.5 years was higher (the former significantly[FIG 2] **[Au: *P* value?]**) than those detected at annual and biennial screening rounds, indicating that a screening interval >24 months might be too long[102].

These studies show the added value of patient stratification on the basis of the results from the baseline LDCT scan; however, this stratification approach leads to questioning of the value of risk assessment before testing. For example, if an individual is already eligible for screening, is further stratification on the basis of the baseline screen a correct approach? If the baseline result was negative, should this patient not have been invited for screening at all? Nevertheless, using the baseline screening result as an additional, independent, lung-cancer risk stratification together with variables specific for each participant to determine eligibility might help to reduce the number of unnecessary screenings[103] (TABLE 1).

[H1] Sex differences in lung cancer

Lung cancer screening trials have revealed differences in lung cancer-specific mortality between men and women. Shortly after the publication of the NLST

mortality results at a median follow-up duration of 7.5 years, a detailed analysis of these results stratified by several factors was presented[104]. In this analysis, lung cancer incidence and mortality was evaluated up to 31 December 2009, instead of 15 January 2009, the date in the original publication[4]. Lung cancer screening was found to be beneficial to a higher extent in women than in men (TABLE 2), although this interaction was not statistically significant (*P* = 0.08). Updated results from the NLST were published after an extended follow-up duration of 11.3 years for lung cancer incidence and 12.3 years for mortality[105], a period in which potential confounding owing to participation in the screening programme would be diluted. The investigators found a beneficial effect for women, with lung-cancer mortality RRs in dilution-adjusted analysis of 0.89 (95% CI 0.80–1.00), 0.95 (95% CI 0.83–1.10) and 0.80 (95% CI 0.66–0.96) in the overall study population, men and women, respectively, although when directly compared, the difference between men and women was not statistically significant. The number of patients with stage IV disease was 468 in the LDCT arm versus 597 in the radiography arm; this difference was larger for women (165 and 232 patients with stage IV disease in the LDCT and radiography arms, respectively) than for men.

The NELSON outcomes published after 10 years of follow up were focused on the effect of screening in male participants, owing to the low number of women involved in the trial (TABLE 2). Nevertheless, lung cancer-specific mortality outcomes were more favourable for women than men, although the 10-year lung cancer-specific mortality results were not statistically significant in women (RR 0.67, 95% CI 0.38–1.14). At 7, 8 and 9 years after baseline LDCT-based screening, the magnitude of lung cancer-specific mortality reduction was greater in women than in men, with RRs of 0.46 (95% CI 0.21–0.96) versus 0.79 (95% CI 0.60–1.03) at 7 years, 0.41

(95% CI 0.19–0.84) versus 0.76 (95% CI 0.60–0.97) at 8 years and 0.52 (95% CI 0.28–0.94) versus 0.76 (95% CI 0.61–0.96) at 9 years. At 11 years, and thus 5.5 years after the last screening round, the RR was 0.78 overall, indicating the importance of repeated screening and the length of screening intervals.

In the LUSI trial, the difference in lung cancer mortality between individuals in the LDCT screening and no screening arms was not statistically significant (HR 0.74, 95% CI 0.46–1.19; *P* = 0.21), possibly owing to the small size of the intervention population (TABLE 2)[6]. However, lung-cancer specific mortality was significantly lower in the screening arm when considering women alone (HR 0.31, 95% CI 0.10–0.96; *P* = 0.04).

Taken together, the sex-specific subgroup analyses of the NLST, NELSON and LUSI trials suggest that lung cancer screening could have a more beneficial effect in women than in men, with trends towards fewer late-stage cancers and fewer lung cancer-related deaths in women undergoing LDCT-based screening. The outcomes of these trials are consistent with estimates of the sensitivity of lung cancer detection and mean preclinical durations established through modelling of the natural history of lung cancer using data from the PLCO trial[106] and other clinical studies. In a Swedish cohort study including >23,000 patients with lung adenocarcinomas (LUADs) or squamous cell carcinomas of the lung, women presented with a better performance status, were younger and more often never-smokers at the time of lung cancer diagnosis compared with men (*P* ≤0.04). Furthermore, women diagnosed with LUAD had a lower comorbidity burden, had tumours of a less advanced stage and a higher proportion of *EGFR*-mutated tumours than men (*P* <0.001). When comparing survival outcomes on the basis of tumour stage at the time of detection, lung cancer-specific survival was consistently less favourable for men than for women, with a HR

of 0.69 (95% CI 0.63–0.76) for stage IA–IIB LUADs and 0.94 (95% CI 0.88–0.99) for stage IIIB–IV LUADs[107]. Similar results from other large-cohort studies, including a study using data from the Surveillance, Epidemiology, and End Results (SEER) database, have shown a beneficial effect of LDCT-based screening on lung cancer-specific survival in women. An analysis of outcomes involving 24,671 men (51.7%) and 23,035 women (48.3%) from this cohort revealed that 5-year lung cancer-specific survival was significantly worse for men than women (HR 1.24, 95% CI 1.20–1.28; *P* <0.001), even after adjusting for age, ethnicity, performance status and smoking status[108]. Future studies could help to establish whether the use of different lung-cancer screening guidelines for men and women could improve screening performance.

[H1] Integrated smoking cessation

Many experts in public health have proposed to integrate smoking-cessation interventions within LDCT-based screening programmes in the future. For example, the EUPS recommends offering advice on smoking cessation to all current smokers[47]. The NLST and UKLS provide evidence on the effect of in-trial events on smoking cessation. In the NLST analysis, individuals were significantly more likely to quit smoking if abnormal results had been observed in the previous year's screen (*P* <0.0001)[109]. Differences in smoking prevalence among participants in the NLST trial were detected up to 5 years after the last screen. Around the same time as the publication of this analysis of the NLST data, results from the Danish Lung Cancer Screening Trial were published. In this trial, 4,104 participants with a smoking history were randomly assigned to undergo annual LDCT-based screening or no screening. At 5 years, no significant differences in annual smoking status were detected

between the LDCT group and control group[110]. In fact, the results of this trial were disappointing because the percentage of ex-smokers in both groups combined significantly increased from 24% at baseline to 37% at year 5 of screening (P <0.001)[110]. The findings from the UKLS trial support those from the NLST trial[111] and are opposed to those from the Danish Lung Cancer Screening Trial. In the UKLS, independent of the screening result, smoking-cessation rates were 8% (36 of 479 individuals) and 14% (75 of 527) in the control and intervention arms, respectively, 2 weeks after baseline scan results or control assignment, and 21% (79 of 377) versus 24% (115 of 488) up to 2 years after recruitment. Participants with a positive screening result were more likely to quit in the longer term compared with those in the control group (P = 0.007) and those receiving a negative result (P <0.001)[111]. This observation raises the question as to whether smoking-cessation programmes are only effective in participants requiring an intervention for cancer and suggest that such programmes might not have been successfully integrated yet into LDCT-based lung cancer screening — addressing this challenge clearly requires further innovative research. The Yorkshire Lung cancer screening trial (UK) has a ground-breaking ongoing study to integrating smoking cessation and CT screening [20]

Kummer et al.[112] have identified different patterns of response to patient participation in screening programmes, both from a psychological and behavioural point of view. Their analysis indicated that the simplistic concept linking smoking cessation with involvement in a CT-based screening programme needs to be reconsidered. These programmes require a more in-depth research agenda to ensure that communication of the screening pathway is designed to promote well-

being, motivate positive behavioural change and, in particular, smoking cessation, ultimately maximizing patient benefit. The fact that lung cancer screening of high-risk participants presents a learning opportunity for smoking cessation should be acknowledged, especially among individuals who receive a positive scan result. Nevertheless, further behavioural research is urgently required to evaluate optimal strategies for integrating smoking-cessation interventions within stratified lung cancer screening, which would lead to further reduction in smoking-related morbidity and mortality.

[H1] Cost effectiveness of lung cancer screening

Any innovative health-care technology — with either curative or preventative intent — requires appraisal from health regulators of its added value. Owing to budget constraints, decision-makers must consider the economic aspects associated with a new technology, analysing the balance between additional costs and health-care benefits through cost-effectiveness analyses. In some countries, innovations such as lung cancer screening might not be introduced if they are not considered cost-effective. Therefore, these analyses can be crucial in discussions of national lung cancer screening programmes. In this context, a cost-effectiveness model would compare a theoretical population that is screened — with all its additional costs, savings and health benefits — with the same population in the absence of screening. Health benefits are expressed as LYs or quality-adjusted (QA) LYs gained. Although screening does not directly create health benefits per se, it enables early detection of lung cancer and thus improved treatment options, which can result in health benefits. In these models, input parameters on costs and health benefits are often required to be country specific, while screening-related parameters (such as efficacy, sensitivity and specificity) are based on data from large screening trials. Results are expressed

as the incremental cost-effectiveness ratio (ICER), reflecting net costs per QALY or LY gained.

Several cost-effectiveness studies on lung cancer screening have been performed using datasets from various specific clinical studies as an input, while accounting for different scenarios[113–124] (FIG. 4). Using country-specific thresholds for cost-effectiveness, most studies have demonstrated that lung cancer screening can be cost-effective, with ICERs of US$15,000–100,000 per QALY gained and $20,000–62,000 per LY gained. For example, ten Haaf et al.[119] considered a scenario in which participants were assumed eligible for screening if they were aged 55–75 years, had smoked >40 pack years and were current smokers or had quit <10 years before the first screen. On the basis of several simulations, lung cancer screening was considered cost-effective against the threshold of CAD$50,000 per QALY. In the UK, a cost-effectiveness model was developed, which was utilised in the UKLS trial[125]. In addition, the UKLS trial investigators reported an estimate cost of ~£8,500 per QALY gained in individuals undergoing screening, although this value was subject to a number of uncertainties[28], as it was only based on the UKLS pilot data.

Both annual and biennial screening programmes have been deemed as potentially cost effective. Goffin et al.[118] specifically compared both strategies in a scenario using the NLST eligibility criteria. They concluded that biennial screening used fewer resources and, although associated with lower gains of LYs, resulted in very similar gains of QALYs over a timeframe of 20 years. These researchers estimated that the ICER of annual compared with biennial screening was US$54,000–4.8 million/QALY gained, which would make biennial screening more cost-effective. However, ten Haaf et al.[119] concluded that annual screening was

more cost-effective than biennial screening, although less-intensive screening with longer intervals could also represent a cost-effective approach.

The situation in the USA, where $100,000 per QALY is considered cost-effective by the federal health-care system (Centers for Medicare & Medicaid Services (CMS)), is very different from that in Europe (50,000 euro or $55,000) and the UK (£20,000–30,000; FIG. 4). Criss et al.[115] developed four models that showed that the NLST, CMS and USPSTF screening strategies were all cost-effective in the USA, with ICERs averaging $49,200, $68,600 and $96,700 per QALY, respectively. The main difference between these strategies is the maximum age at which to stop screening (80 years, 77 years and 74 years, respectively). This analysis highlighted exactly where the costs lay and the five greatest areas contributing to the total costs associated with screening programmes, noting that the major one is the actual LDCT screening itself. Nevertheless, the major limitation of this analysis was that risk prediction models for the selection of participants, which could potentially increase the cost-effectiveness of screening, were not factored in. The authors indicated their plan to address this aspect in future projects from the Cancer Intervention and Surveillance Modeling Network. While using a risk prediction model can increase the cost-effectiveness of a screening programme, related issues that have not been investigated in this context include the tendency of the target population to have comorbidities and therefore a shorter life expectancy and potentially a lower quality of life. The latest publication of results from the NELSON trial warrants new cost-effectiveness analyses to assess the financial implications of volumetric-based lung screening[10]. The increased availability of data from patients with lung cancer and, in particular, from screening programmes, will make future cost-effectiveness analyses more robust and therefore better suited to assist

decision-makers on designing and introducing LDCT-based lung-cancer screening in national programmes. Future cost-effectiveness models could encompass multiple perspectives, such as the health-care and societal perspectives, as well as a fiscal perspective to better determine the financial implications of introducing national lung-cancer screening programmes. Future cost-effectiveness models should also take into account the costs of expensive targeted agents and immune-checkpoint inhibitors.

[H1] Current opportunities worldwide

[H2] Screening in China

Lung cancer has been the leading cause of cancer-related death in China since 2005, with an age-standardized 5-year survival of only 19.7% in 2015[126]. Data from the National Central Cancer Registry of China (NCCRC) in 2014revealed that, on average, >10,400 lung cancers were diagnosed daily and >6,200 lung cancer-related deaths occurred each day[127]. Lung cancer mortality in China has been projected to increase by ~40% between 2015–2030[128]. Compared with countries in Europe and North America, in most Asian countries lung cancer is more frequent even in non-smokers[129], suggesting that Asian countries might need to use lung-cancer screening guidelines different from those we have discussed in previous sections.

One of the earliest lung cancer screening programmes in China was initiated in 2009 and involved a rural population in the Yunnan Province[130]. Since 2012, the Ministries of Finance and Health of China have included lung cancer screening in the national cancer early detection and treatment programme for the urban population[129]. A modelling study revealed that LDCT-based screening in urban

areas of China would lead to a 17.2% and 24.2% reduction of lung cancer-related mortality compared with chest radiography-based screening and no screening, respectively[131]. In Shanghai, a total of 14,506 individuals were involved in an LDCT-based lung cancer screening study[132]. The preset positive result of screening was defined as nodules of any size and any density. The lung cancer detection and incidental detection (that is, detection of any abnormality other than lung cancer) rates were 29.9% and 1.2%, respectively, with an incidental detection rate of stage I lung cancer of 0.97%. The frequency of detection of nodules with a diameter <5 mm was 74.9%, although 94.1% lung cancers detected were ≥5 mm, and the frequency of detection of non-solid nodules was 84.9%. Therefore, the baseline LDCT-based lung cancer screening round revealed that subsolid nodules accounted for the majority of lung cancers in the study population and that a diameter of 5 mm is the recommended threshold for positive results[132].

LDCT-based lung cancer screening has gained popularity in China; however the definition of the high-risk population and the high number of false-positive results remain two challenges that need to be addressed. Previous studies have shown that the criteria used in Europe and North America to determine individuals at a high risk of lung cancer might not be suitable for the Chinese population, especially considering the high incidence of lung cancer in females and non-smokers in China[133]. Optimization of the eligibility criteria and identification of (new) risk factors associated with lung nodule detection are crucial aspects for improving the sensitivity and specificity of LDCT-based lung cancer screening in China. The definition of high-risk criteria in the screening population will depend on the results of future and ongoing multicentre RCTs. Considering the geographic and lifestyle variations across the country, specific high-risk criteria for the major regions might

need to be proposed to account for differences in external high-risk factors, such as exposure to air pollution in the afternoon, to radon (indoors), kitchen fumes and secondhand smoke. Family history and genetic susceptibility should also be considered. Identifying subpopulations at high risk of lung cancer, should be a clear priority in China, because no large epidemiological data sets have thus far been used to assess risk parameters for screening eligibility.

The challenge posed by the high-number of false-positive results is mainly caused by cultural perceptions. In our experience (SY.L.), the medical environment of China tends to favour cautiousness from both clinicians and patients, which could result in overtreatment. A large number of small or intermediate sized (<5 mm) lung nodules that are detected in >75% of all participants turned out to be benign [132]; however, this result increases apprehension in the general population. Currently, the number of nodules with a diameter <3 mm detected is increasing, especially with the development of AI-based approaches; even for these small nodules, in practice invasive treatment is often preferred over watchful waiting.

An extensive review of lung cancer screening in China published in 2019[129] demonstrated a great deal of lung cancer screening activity throughout the country. Most of these programmes, however, have reported only preliminary results, mainly through websites and meeting abstracts, and thus, the available data need to be interpreted cautiously. The authors of this Review have reported that 23 lung-cancer screening programmes have been completed or are ongoing in China since the 1980s, mainly after 2000[129]. Of note, the entry criteria are generally not smoking-stringent owing to the existence of different lung cancer high-risk subpopulations in China. In this country, the evidence for LDCT-based screening implementation is mainly based on results of RCTs conducted elsewhere. Looking into the future,

LDCT-based screening programmes incorporating smoking cessation would result in greater benefits for participants. The recommendations advocated in this extensive Review of lung cancer screening in China are pertinent to future success and need to be implemented[129] (Supplementary Table 1). Further research in China, where lung cancer is now considered an epidemic, is urgently required.

[H2] Screening in Japan and South Korea

To date, few studies have reported on the efficacy of LDCT-based lung cancer screening in non-smokers and light-smokers[134]. In Japan, one such study was initiated in the Hitachi district which included a large proportion (~30%) of individuals aged 50–64 years with a smoking history of <30 pack-years[135,136]. Lung cancer mortality in this district following screening was found to differ significantly with that in the whole of Japan (2005–2009), with a standardized mortality ratio of 0.76 (95% CI 0.67–0.86; *P* <0.001). In women, the reduction in standardized mortality ratio was also significant (0.74, 95% CI 0.56–0.97); of note, ≥90% of women were non-smokers[135]. These results suggest that LDCT-based screening can lead to a decline in lung cancer-related mortality both in non-smokers and smokers, although Sagawa and colleagues identified a number of limitations in this study, such as trial design, with CT scans only in year 1 and year 6.

The National Korean Lung Cancer Screening Project (K-LUCAS) is a single-arm trial aimed at a high-risk population of individuals[137]. The pilot study included 256 individuals and its purpose was to assess the feasibility of a multicentre nationwide programme using the K-LUCAS protocol[137]. The inclusion criteria for K-LUCAS were 55–74 years of age, current or former smokers (who had quit smoking <15 years) and ≥30 pack-years smoking history. In a pilot test of this trial involving

256 participants, 10 nodules classified as grade 3 according to Lung-RADS were identified, 9 grade 4 nodules were identified and one participant was diagnosed with lung cancer. In addition, 86.3% of participants said they would participate in future lung cancer screening programmes and the average degree of willingness to quit smoking among current smokers was 12.7% higher than before screening.

[H1] Future opportunities using AI

The implementation of large lung cancer screening programmes has led to a massive increase in the workload of radiologists[138]. In parallel, technical improvements in LDCT have enabled small-sized pulmonary nodules to be visualized. Over the past decades, efforts have been made to improve screening procedures using AI-based strategies to detect and classify pulmonary nodules. Before these algorithms are implemented in routine clinical care, their performance should be proven to be robust in external datasets.

[H2] Computer-aided detection systems

Different CAD systems have been developed to assist radiologists in identifying relevant nodules. The use of CAD, however, remains challenging. A volumetric chest LDCT scan contains >9 million voxels. A lung nodule with a diameter of 5 mm occupies ~130 voxels, or only $1.4x10^{-5}$ of the lung volume[139]. False-negative results (when a clinically significant nodule is not detected) and especially false-positive findings can be common; adding the result of CAD-based assessment to that of a radiologist led to a significantly better performance that from combining of two CAD systems without a human reader (97–99% versus 85–88%; P <0.03)[140].

The effect of CAD as a second reader has been studied in different LDCT-based lung cancer screening trials. Within a subset of 400 patients from the NELSON trial that had been double-read by radiologists, 22% of nodules ≥50 mm^3 were identified solely by CAD, including one lung cancer[141]. Liang et al. showed that four different CAD systems enabled the identification of 56–70% of 50 tumours (with a mean diameter of 4.8 mm) that had been missed on the prevalence round of the I-ELCAP study, but failed to identify 20% of lung cancers identified by radiologists[142]. These results suggest that CAD has potential value as a second reader in LDCT-based lung cancer screening, although this approach is currently not currently part of routine clinical care. The detection rate of current standard LDCT was evaluated using maximum-intensity-projection (MIP; a type of CAD) or two different CAD systems. These systems were associated with comparable incremental sensitivity, with reporting times and false-positive rates favouring MIP[143,144]. Unlike the capabilities of radiologists, however, CAD systems keep being substantially improved over time owing to advances in neural network and AI systems[143,145], and thus these systems might have a role in lung cancer screening in the future.

[H2] Lung nodule classification

Deep learning (DL)-based approaches can help to accurately distinguish benign from malignant lung nodules, as reported in two large-cohort studies published in 2019[146,147]. Ardila et al. estimated lung cancer risk with a DL approach mainly based on changes in nodule volume[146]. The training set and test set included data from 42,290 and 6,716 NLST participants, respectively, and the algorithm was validated retrospectively in an independent clinical dataset including 1,139

individuals[146]. Lung cancer risk estimation was restricted to 1-year after LDCT. For the 6,716 participants (including 86 with cancer) in the test set, the model achieved an AUC of 94.4% (95% CI 91.1–97.3%). A similar result was achieved in the external validation set (1,139 individuals, 27 with cancer), with an AUC of 95.5% (95% CI 83.1–98.0%). Huang et al.[147] focused on nodule classification at the annual follow-up scan rather than at the baseline LDCT scan. Using a DL algorithm (referred to as DeepLR), they identified nodule features predictive of malignancy. For the training set, they used baseline and follow-up LDCT data from 25,097 NLST participants who had undergone at least two LDCT scans. DeepLR was validated in 2,294 participants from the PanCan study; among this high-risk population, the algorithm enabled to identify a low-risk group (55%) with an estimated probability of developing lung cancer in the following 2 years of only 0.2%. DeepLR outperformed Lung-RADS in predicting lung cancer-related mortality risk (HR 16.07, 95% CI 10.15–25.44; *P* <0.0001). In addition, DeepLR was associated with a very high true-negative nodule rate, which could enable the potential identification of individuals who would benefit from repeat screening every 2–3 years as opposed to the current recommendation of annual screening[147].

Baldwin et al.[148] compared the performance of an AI-based algorithm, the Lung Cancer Prediction Convolutional Neural Network (LCP-CNN), with that of the Brock parsimonious model in discriminating between benign and malignant pulmonary nodules. Three radiology datasets from the UK were used in this analysis, which revealed AUCs of 89.6% and 86.8% for the LCP-CNN and the Brock parsimonious model, respectively ($P \leq 0.005$). The percentage of nodules with a score below the lowest category for cancer, and thus not requiring short-term follow-up, were 24.5% and 10.9%, respectively. Of note, this study was performed on a

clinical trial dataset with a lung cancer prevalence of 19.3%, which is in contrast with the prevalence typical in lung cancer screening settings (1–3%) and thus, the performance of LCP-CNN in a screening setting is currently unknown.

AI also has potential to enable the discrimination of different types of lung nodules. A total of 12,754 thin-section chest LDCT scans were retrospectively collected for training, validation and testing of DL-based convolutional neural network (CNN). Pulmonary nodules from these scans were categorized into four types: solid, subsolid, calcified and pleural. The DL model enabled the detection of most of the nodules when choosing a low-specificity standard. This model had a sensitivity and specificity of 99.57 (95% CI 98.62–100.00) and a specificity of 28.03 (95% CI 25.51–30.62) compared with 97.44 (95% CI 95.26–99.18) and 29.23 (95% CI 26.69–31.88), respectively, using the Brock parsimonious model. The success of this model relied on the combination of two CNN structures[149].

[H1] Conclusions

The results from several RCTs of LDCT-based lung cancer screening, including NELSON, have now provided conclusive evidence of a mortality reduction associated with the implementation of lung cancer screening in individuals from both sexes deemed at a high risk of lung cancer[10,150]. The lung cancer community now has the opportunity to focus on implementation research, guided by objectives that we have identified thanks to the advances of the past decade (BOX 1). The results of these research programmes will help to consolidate international opinion and guide national policy-makers in designing the most appropriate lung cancer screening programmes which are cost effective for their own diverse health-care systems.

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Author contributions

M.O. contributed to all aspects of the preparation of this article. S.L. and J.E.W. researched data, M.A.H. contributed to discussions, researched data and supported the draft of the manuscript. J.K.F. contributed to all aspects of the preparation of this article. The final manuscript was approved by all authors.

Competing interests

The authors declare no competing interests.

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Key points

FIG. 1 | Screening Planning and Implementation RAtionale for Lung cancer. Herein we present a framework to define the scope of future implementation research on lung cancer screening programmes, referred to as Screening Planning and Implementation RAtionale for Lung cancer (SPIRAL).

FIG. 2 | Randomized controlled trials of LDCT-based approaches to lung cancer screening. Timeline of randomized-controlled trials (RCTs) of low-dose computer tomography (LDCT)-based lung-cancer screening, showing time from the recruitment date to the end of follow up and relevant findings associated with each trial. Of note, the mortality data are expressed with a *P* value excepting for all RCT excepting NELSON, for which confidence levels are provided. CXR, chest radiography; LDCT, low-dose computer tomography; PY, packet years; vs, versus; yr, years. [a]RCTs performing CT volumetry.

FIG. 3 | Risk-stratification protocols for LDCT scan-detected lung nodules. a | Non-calcified solid nodules detected at baseline low-dose computer tomography (LDCT) scans. b | New non-calcified solid nodules detected after baseline LDCT scans. c | Non-calcified subsolid nodules detected at baseline or new nodules detected after the baseline scan. These protocols are based on the data from the NELSON trial (Publication Ref). d, days; VDT, volume-doubling time; vs, versus.

FIG. 4 | Cost effectiveness of LDCT-based lung cancer screening. Selected published cost-effectiveness analyses of low-dose computed tomography (LDCT)-based lung cancer screening[113–124], with results showing incremental cost-effectiveness ratios (ICER) per quality-adjusted life-years (QALY) or per life-years gained (LYG). The studies are sorted by country, and country-specific thresholds for willingness to pay (WTP) are provided. Data are presented in US$ (with conversion, if necessary) and adjusted to reflect pricing levels in 2019. These studies show LDCT-based lung cancer screening can be considered cost-effective in most scenarios.

FIG. 5 | Fifty-year timeline of lung cancer LDCT-based screening and implementation planning. Evidence-based lung cancer screening trials started in the 1970s with trials of chest radiography (CXR)and continued with the pioneering work in low-dose computed tomography (LDCT) undertaken in the International Early Lung Cancer Action Project (I-ELCAP), the US National Lung Screening Trial (NLST) and seven pilot trials in Europe. Recruitment for the NELSON trial recruitment, the only fully powered lung cancer LDCT-based screening trial in Europe, started in 2003. These five decades of research have now provided the lung cancer community with an international framework for the implementation of lung cancer LDCT-based screening. RCT, randomized controlled trial; vs, versus.

Box 1 | Guiding principles for implementation research in lung cancer screening (FIG. 5).

- Optimize low-dose computed tomography (LDCT)-based lung cancer screening by evaluating the cost-effectiveness of existing as well as innovative approaches on the basis of risk estimates.
- Identify the optimal and most cost-effective strategy for inviting high-risk individuals (often hard to reach) to participate in population-focused LDCT-based lung-cancer screening interventions.
- Estimate the effect of personalized, less-intensive screening regimens with longer screening intervals (for example, biennial) relying on health-related risk factors detected on baseline LDCT scan and, potentially, on blood-based biomarker assays.
- Explore the effect of integrating effective smoking-cessation interventions within lung-cancer screening programmes.
- Estimate the long-term health outcomes, including benefits and harms, as well as cost-effectiveness by incorporating the above recommendations.
- Develop guidelines and training programmes to facilitate implementation of evidence-based, quality-assured LDCT-based lung cancer screening and also appropriate management of LDCT screen-detected pulmonary nodules.

Table 1 | Lung cancer risk stratification on the basis of baseline and follow-up low-dose CT screens

Risk category[a]	**Lesions detected**[b]	**Recommendation**
Intermediate-to-high risk of lung cancer (<1%)	No baseline nodule No new nodule at follow-up screening Solid baseline nodule <100 mm^3 or <5 mm New solid nodule <30 mm^3 or <4 mm	Consider prolonged screening interval of up to 24 months
High risk of lung cancer (~3%)	Solid baseline nodule 100–300 mm^3 or 5–10 mm New solid nodule 30–200 mm^3 or 4–8 mm Growing solid nodule with VDT of 400–600 days Subsolid nodule, baseline or new, of any size[c]	Short-term follow-up (3 months) If negative: annual screening
Very high risk of lung cancer (>15%)	Solid baseline nodule >300 mm^3 or >10 mm New solid nodule >200 mm^3 or >8 mm Growing solid nodule with VDT <400 days Subsolid nodule that is growing or has an altered morphology	Referral to MDT for workup If negative: annual screening

MDT, multidisciplinary team; VDT, volume-doubling time. [a]2-year probability of lung cancer, based on largest or fastest-growing nodule. [b]Size expressed as volume (mm^3) or longest diameter (mm). [c]In case of negative follow-up CT scan (no growth), consider prolonged screening interval up to 24 months. Adapted from ref.91.

Table 2 | Results of randomized controlled trial of lung cancer screening stratified by sex.

Study	Median follow up	Outcomes in male participants	Outcomes in female participants
NLST[104]	7.5 years after baseline scan	Screening arm: 311 lung cancer-related deaths among 15,769 individuals (2.0%) No-screening arm: 337 lung cancer-related deaths among 15,761individuals (2.1%) RR 0.92 (95% CI 0.8–1.08)[a]	Screening arm: 158 lung cancer-related deaths among 10,953 individuals (1.4%) No-screening arm: 10,969 individuals 215 lung cancer-related deaths among 10,969 individuals (2.0%) RR 0.73 (95% CI 0.6–0.9)[a]
NLST[105]	11.3 years after baseline (incidence) 12.3 years after baseline (mortality)	Screening arm: 733 lung cancer-related deaths among 15,769 individuals (4.6%) No-screening arm:755 lung cancer-related deaths among 15,761 individuals (4.8%) RR 0.97 (95% CI 0.87–1.07)[a]	Screening arm: 414 lung cancer-related deaths among 10,953 individuals (3.8%) No-screening arm: 481 lung cancer-related deaths among 10,969 individuals (4.4%) RR 0.86 (95% CI 0.75–0.98)[a]
NELSON[10]	10 years after baseline	Screening arm: 341 lung cancers detected in 6,583 individuals (5.2%) 156 lung cancer-related deaths in 6,583 individuals (2.4%) No-screening arm: 304 lung cancers detected in 6,612 individuals 206 lung cancer-related deaths in 6,612 individuals (3.1%) RR 0.76 (0.61–0.94)[a]	Screening arm: Lung cancers detected: NA 25 lung cancer-related deaths in 1,317 individuals (1.9%) No-screening arm: 36 lung cancer-related deaths in 1,277 individuals (2.8%) RR 0.67 (0.38–1.14)[a]

LUSI[6]	7 years after baseline	Screening arm: 43 lung cancers detected among 1,315 individuals (3.3%) 18 lung cancer-related deaths among 1,315 individuals (1.4%) No-screening arm: 19 lung cancer-related deaths among 1,307 individuals (1.5%) HR 0.94 (95% CI 0.54–1.61)[a]	Screening arm: 20 lung cancers detected among 714 individuals (2.8%) 2 lung cancer-related deaths among 714 individuals (0.3%) No screening arm: 10 lung cancer-related deaths among 716 individuals (1.4%) HR 0.31 (95% CI 0.10–0.96)[a]

HR, hazard ratio; NA, not applicable; RR, rate ratio. [a]Values not adjusted for person years.

Supplementary Information

Supplementary Table 1 | Recommendations for implementation of lung cancer screening in China. (Reproduced from Cheng et al.[121])

1. Screening programme coverage to be expanded to underserved areas. Recruitment criteria suggested by other countries should be considered. The involvement of international investigators in lung cancer screening trials in China should be considered.
2. Community-based recruitment may be a more favourable approach in China: utilising face-to-face clinical appointments and trustworthy collaborations with local clinics/ organisations.
3. To make cohort profiles or study protocols public is suggested. Collaboration between lung cancer screening trial groups should be considered. Developing consensus protocols and also the agreement to utilise common databases and minimum datasets would enable pooling of data from different trials in China.
4. In China, consider adapting the entry criteria, i.e. a lower threshold of smoking exposure; consider including other risk factors: second-hand smoke, family history of cancer, occupation and indoor/outdoor air pollution (the latter requires a harmonised approach).
5. Risk-based selection of eligible participants for study entry into lung cancer CT screening programmes (e.g. risk prediction modelling) would be advisable.
6. The current Chinese risk models (for either individual risk or nodule malignancy prediction) should be validated externally, especially in an ongoing lung cancer LDCT screening programme, which could help to confirm the efficacy and effectiveness in the real world. Further optimisation may be integrated over time, i.e. integration with liquid biomarkers and genetic factors.
7. Development of new risk prediction models, specifically for the Chinese population, should be priority, utilising optimal data sources.
8. Cost-effectiveness analysis of all current CT screening programmes should be undertaken, taking into consideration the selection criteria/risk threshold utilised, which would achieve the maximum net benefits over harms.
9. Evaluation of related parameters involved in the screening programmes requires further research in China, e.g. screening interval, screening length, nodule management.
10. Lung cancer screening programmes should be integrated with tobacco control strategies. An a priori design and a detailed record on participants' behaviours/perspectives and study costs including personnel cost, is required for cost-effectiveness evaluation.

Figure 1 Lung cancer Screening Spiral of Ambition.

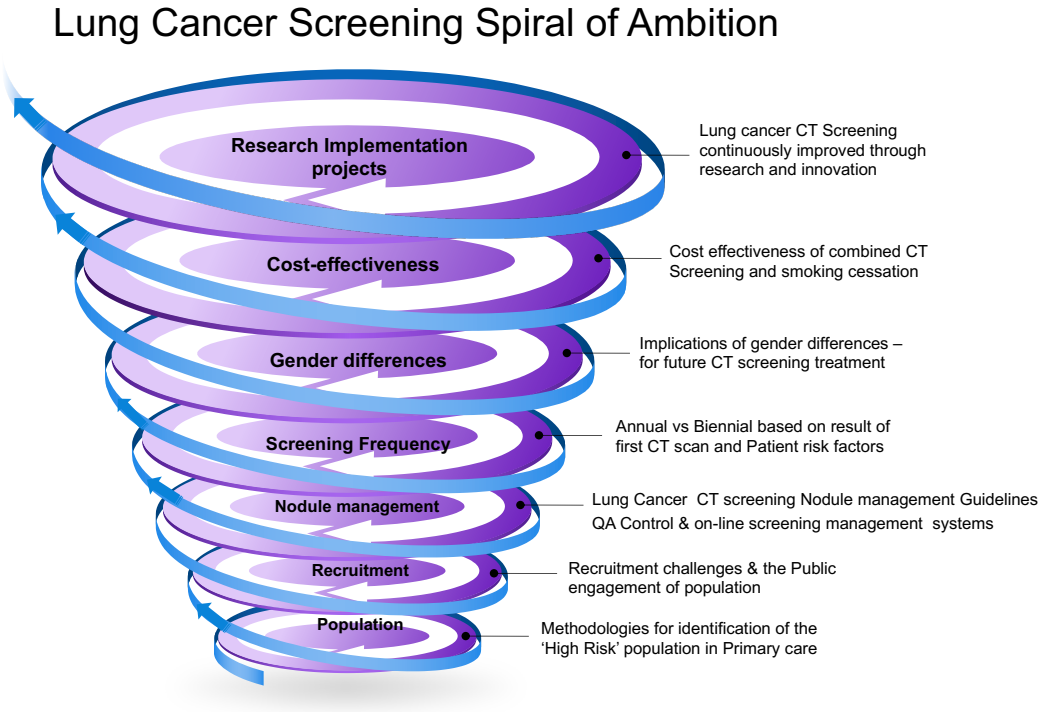


Figure 2

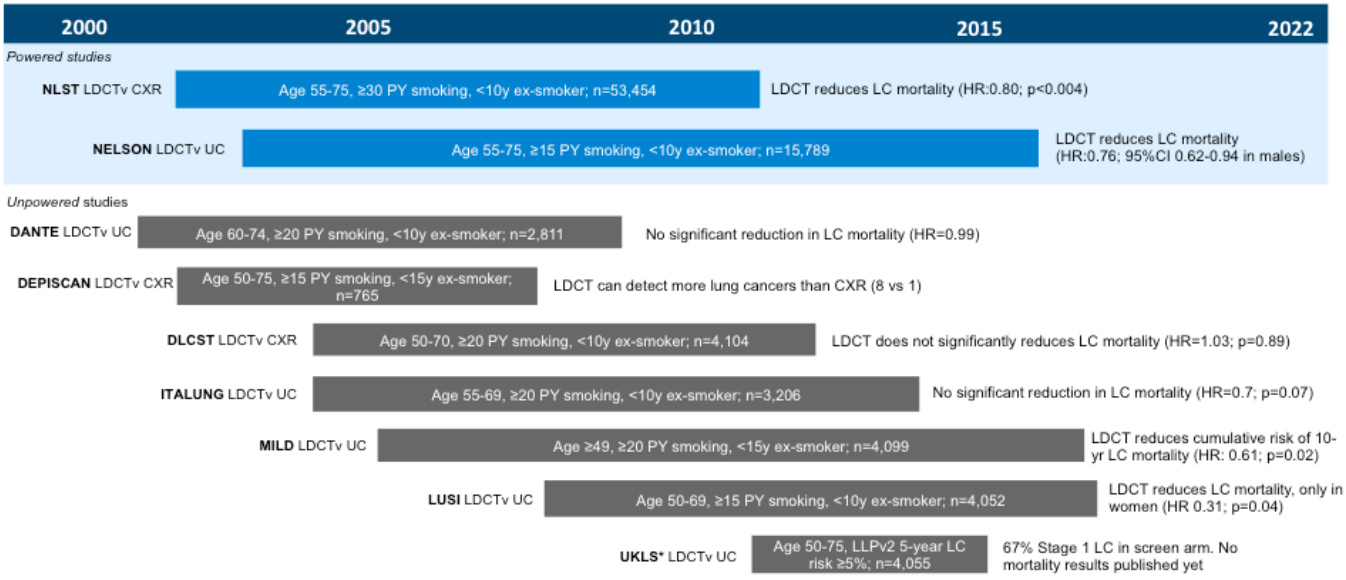

2000
2005
2010
2015
2022
Powered studies
NLST LDCTv CXR
Age 55-75, ≥30 PY smoking, <10y ex-smoker; n=53,454
LDCT reduces LC mortality (HR:0.80; p<0.004)
NELSON LDCTv UC
Age 55-75, ≥15 PY smoking, <10y ex-smoker; n=15,789
LDCT reduces LC mortality (HR:0.76; 95%CI 0.62-0.94 in males)
Unpowered studies
DANTE LDCTv UC
Age 60-74, ≥20 PY smoking, <10y ex-smoker; n=2,811
No significant reduction in LC mortality (HR=0.99)
DEPISCAN LDCTv CXR
Age 50-75, ≥15 PY smoking, <15y ex-smoker; n=765
LDCT can detect more lung cancers than CXR (8 vs 1)
DLCST LDCTv CXR
Age 50-70, ≥20 PY smoking, <10y ex-smoker; n=4,104
LDCT does not significantly reduces LC mortality (HR=1.03; p=0.89)
ITALUNG LDCTv UC
Age 55-69, ≥20 PY smoking, <10y ex-smoker; n=3,206
No significant reduction in LC mortality (HR=0.7; p=0.07)
MILD LDCTv UC
Age ≥49, ≥20 PY smoking, <15y ex-smoker; n=4,099
LDCT reduces cumulative risk of 10-yr LC mortality (HR: 0.61; p=0.02)
LUSI LDCTv UC
Age 50-69, ≥15 PY smoking, <10y ex-smoker; n=4,052
LDCT reduces LC mortality, only in women (HR 0.31; p=0.04)
UKLS* LDCTv UC
Age 50-75, LLPv2 5-year LC risk ≥5%; n=4,055
67% Stage 1 LC in screen arm. No mortality results published yet

Figure 3a Non-calcified solid nodule at baseline LDCT

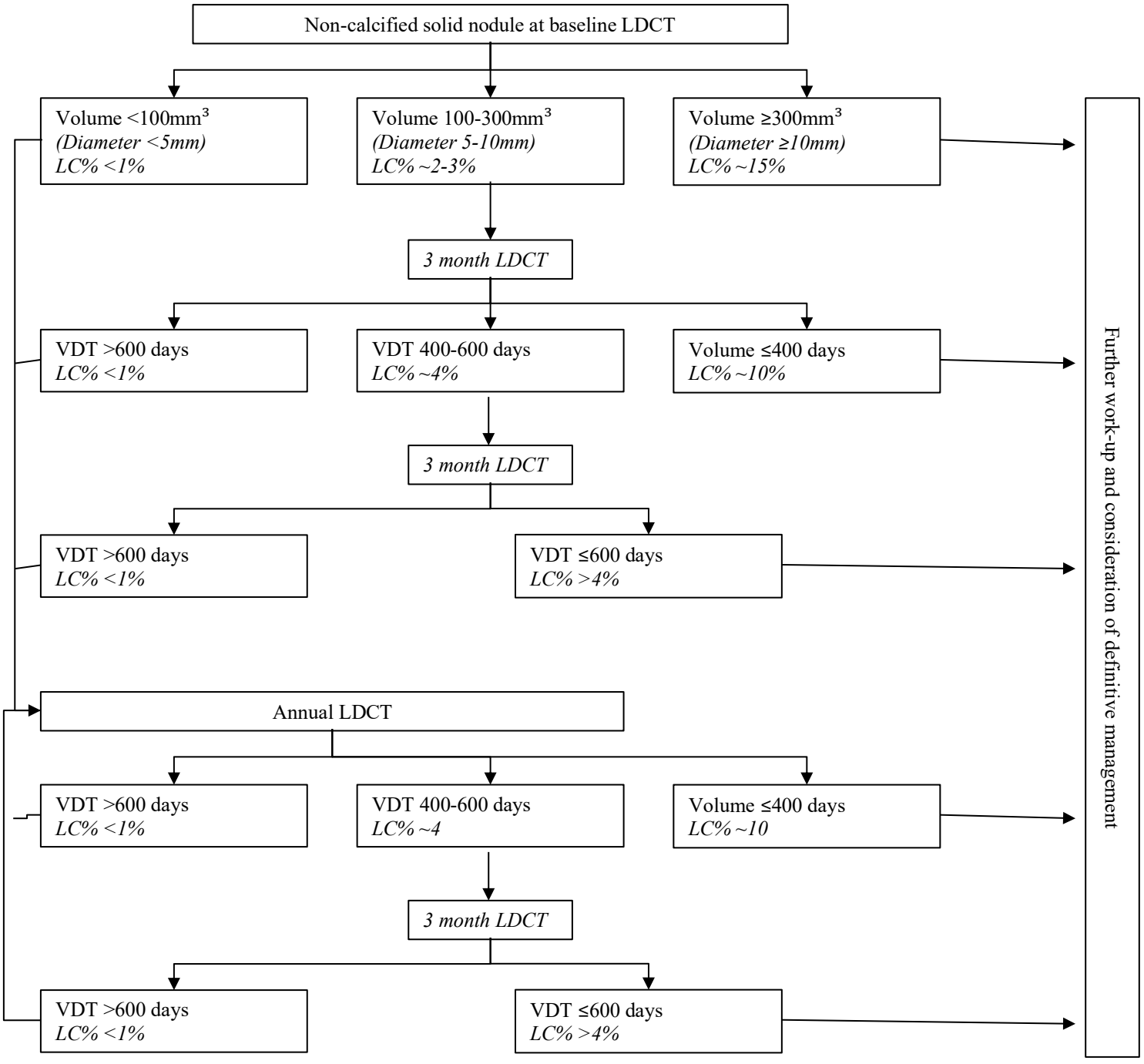


Figure 3b New non-calcified solid nodule after baseline LDCT

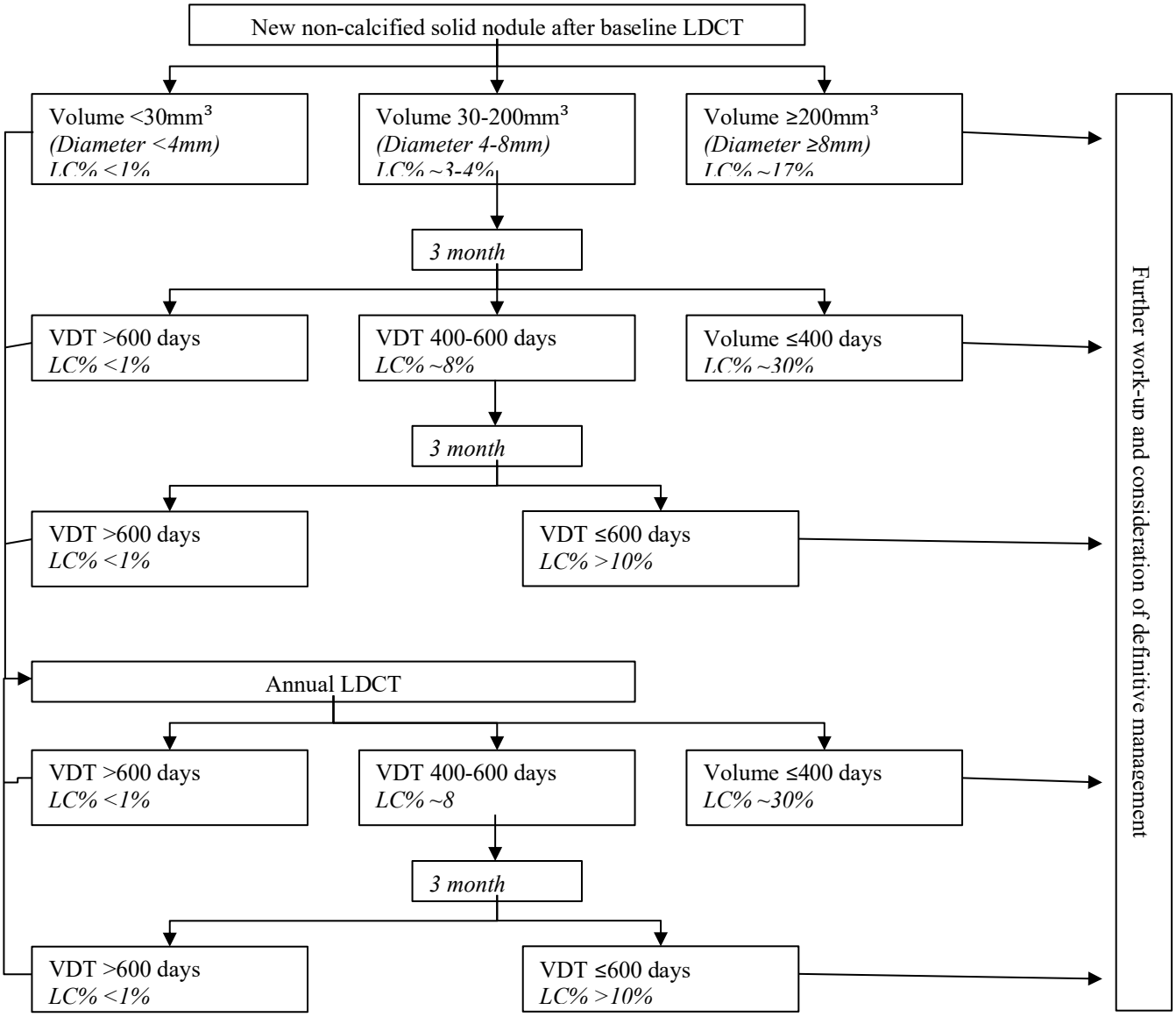


Figure 3c Non-calcified subsolid nodule at baseline or new after baseline

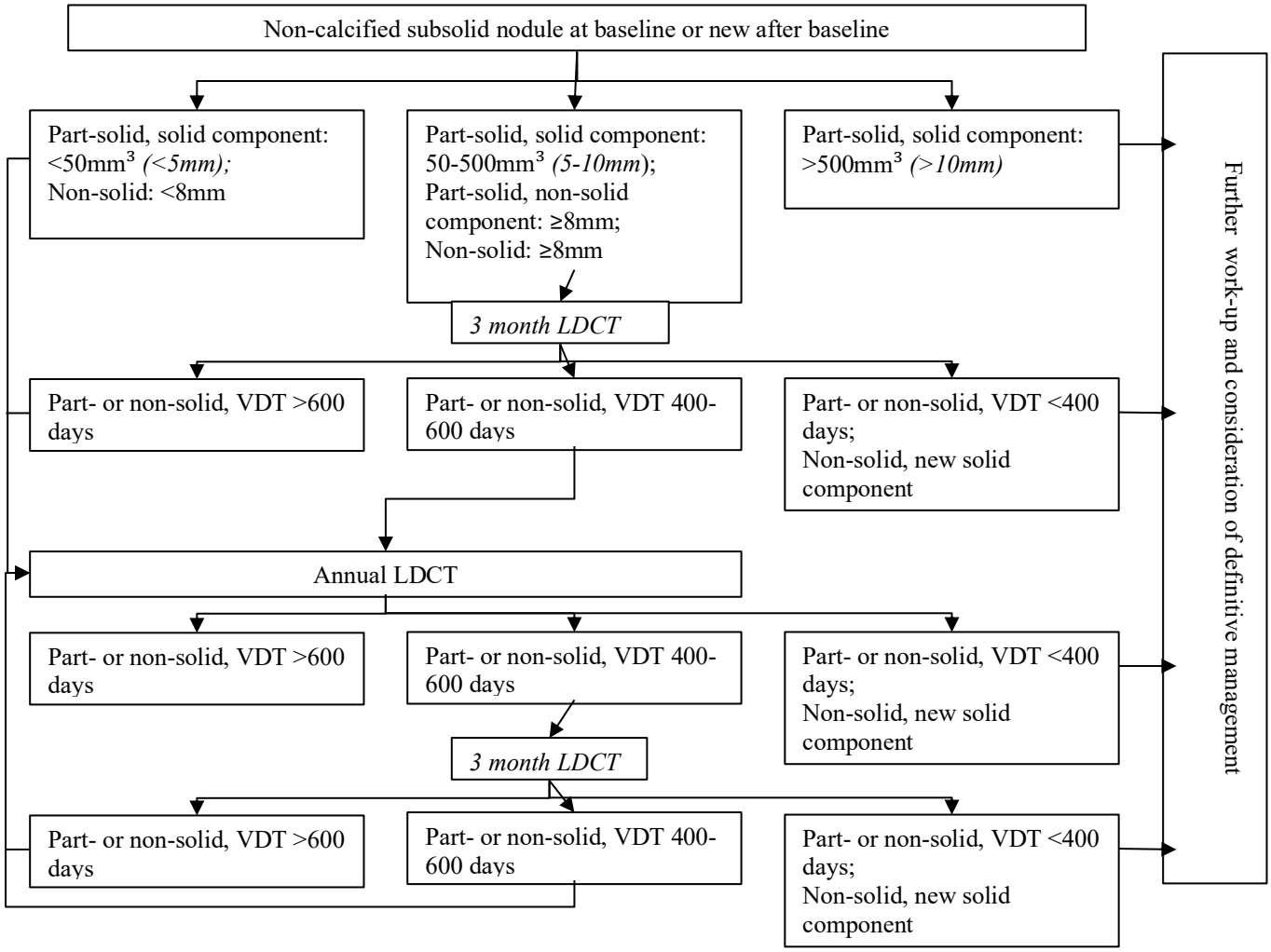
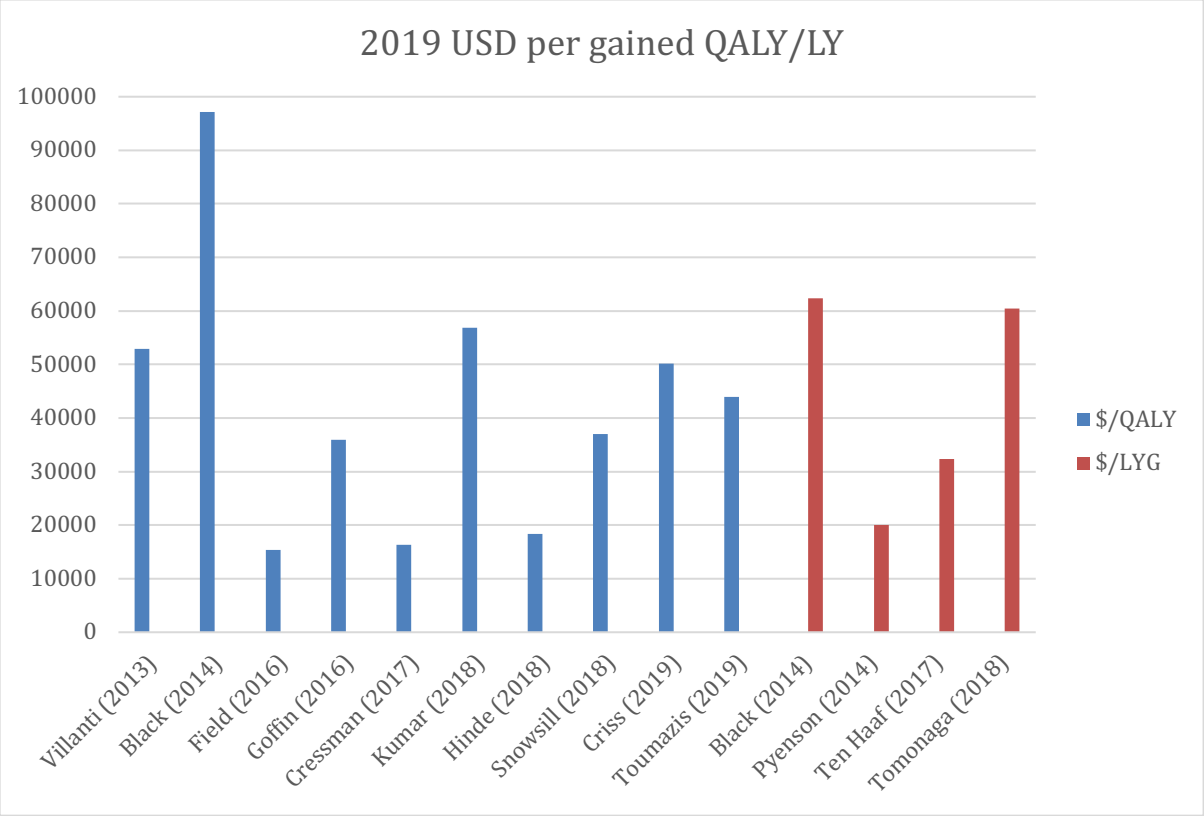


Figure 4 Incremental cost-effectiveness ratios (ICER) per quality-adjusted life-years (QALY) and life-year gained (LYG).



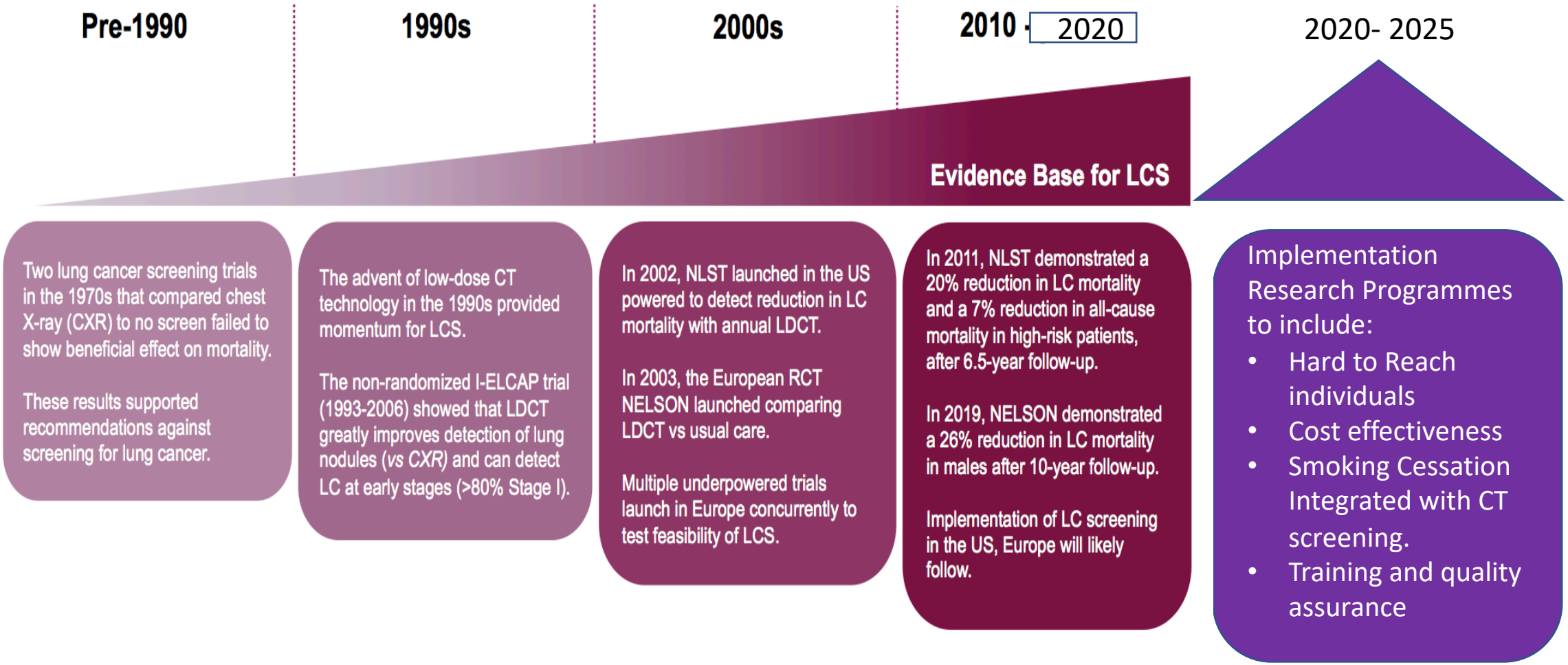

Pre-1990
1990s
2000s
2010 - 2020
2020- 2025
Evidence Base for LCS
Two lung cancer screening trials in the 1970s that compared chest X-ray (CXR) to no screen failed to show beneficial effect on mortality.
These results supported recommendations against screening for lung cancer.
The advent of low-dose CT technology in the 1990s provided momentum for LCS.
The non-randomized I-ELCAP trial (1993-2006) showed that LDCT greatly improves detection of lung nodules (vs CXR) and can detect LC at early stages (>80% Stage I).
In 2002, NLST launched in the US powered to detect reduction in LC mortality with annual LDCT.
In 2003, the European RCT NELSON launched comparing LDCT vs usual care.
Multiple underpowered trials launch in Europe concurrently to test feasibility of LCS.
In 2011, NLST demonstrated a 20% reduction in LC mortality and a 7% reduction in all-cause mortality in high-risk patients, after 6.5-year follow-up.
In 2019, NELSON demonstrated a 26% reduction in LC mortality in males after 10-year follow-up.
Implementation of LC screening in the US, Europe will likely follow.
Implementation Research Programmes to include:
• Hard to Reach individuals
• Cost effectiveness
• Smoking Cessation Integrated with CT screening.
• Training and quality assurance

Table 1 Risk stratification based on the baseline and follow-up CT

Intermediate-high lung cancer risk (<1%) *Consider prolonged screening interval up to 24 months*	**High lung cancer risk (±3%)** *Short-term follow-up (3 months), if negative: annual screening*	**Very high lung cancer risk (>15%)** *Referral to MDT for workup, if negative: annual screening*
No baseline nodule	Solid baseline nodule 100 – 300 mm^3 or 5 – 10 mm	Solid baseline nodule >300 mm^3 or >10 mm
No new nodule at follow-up screening	New solid nodule 30 – 200 mm^3 or 4 – 8 mm	New solid nodule >200 mm^3 or >8 mm
Solid baseline nodule <100 mm^3 or <5 mm	Growing solid nodule VDT 400-600 days	Growing solid nodule VDT<400 days
New solid nodule <30 mm^3 or <4 mm	Subsolid nodule, baseline or new, any size*	Subsolid nodule showing growth or altered morphology

Note: Two-year lung cancer probability, based on largest or fastest-growing nodule

MDT = multidisciplinary team, VDT = volume-doubling time

*in case of negative follow-up CT (no growth), consider prolonged screening interval up to 24 months

Table 2 Results of randomized-controlled lung cancer screening trials stratified by gender.

Study		**Men**	**Women**
NLST*[96]	*N (%)*	15,769 (59)	10,953 (41)
	LC, N (%)	NA	NA
	LC mortality, N (%)	311 (2.0)	158 (1.4)
	LC mortality controls	337/15,761 (2.1)	215/10,969 (2.0)
	RR (95% CI)	0.92 (0.8–1.08)	0.73 (0.6–0.9)
NLST**[97]	*N (%)*	15,769 (59)	10,953 (41)
	LC, N (%)	NA	NA
	LC mortality, N (%)	733 (4.6)	414 (3.8)
	LC mortality controls	755/15,761 (4.8)	481/10,969 (4.4)
	RR (95% CI)	0.97 (0.87–1.07)	0.86 (0.75–0.98)
NELSON***[9]	*N (%)*	6,583 (83.3)	1,317 (16.7)
	LC, N (%)	341 (5.2)	NA
	LC mortality, N (%)	156 (2.4)	25(1.9)
	LC mortality controls	206/6,612 (3.1)	36/1,277 (2.8)
	RR (95% CI)	0.76 (0.61-0.94)	0.67 (0.38-1.14)
LUSI****[5]	*N (%)*	1,315 (64.8)	714 (35.2)
	LC, N (%)	43 (3.3)	20 (2.8)
	LC mortality, N (%)	18 (1.4)	2 (0.3)
	LC mortality controls	19/1,307 (1.5)	10/716 (1.4)
	HR (95% CI)	0.94 (0.54–1.61)	0.31 (0.10–0.96)

Note: numbers in this table were not adjusted for person years
Abbreviations: CI = confidence interval, HR = hazard ratio, LC = lung cancer, LUSI = German Lung cancer Screening Intervention trial, NA = not applicable, NELSON = Dutch-Belgian randomized-controlled lung cancer screening trial, NLST = national lung cancer screening trial, RR= rate ratio.
* median follow-up 7.5 years after baseline
** median follow-up 11.3 years after baseline (incidence), 12.3 years after baseline (mortality)
*** median follow-up 10 years after baseline
**** median follow-up 7 years after baseline

Supplementary Information

Table S1

Recommendations for implementation of lung cancer screening in China
(Reproduced from Cheng et al.[123])

1. Screening programme coverage to be expanded to underserved areas. Recruitment criteria suggested by other countries should be considered. The involvement of international investigators in lung cancer screening trials in China should be considered.

2. Community-based recruitment may be a more favourable approach in China: utilising face-to-face clinical appointments and trustworthy collaborations with local clinics/ organisations.

3. To make cohort profiles or study protocols public is suggested. Collaboration between lung cancer screening trial groups should be considered. Developing consensus protocols and also the agreement to utilise common databases and minimum datasets would enable pooling of data from different trials in China.

4. In China, consider adapting the entry criteria, i.e. a lower threshold of smoking exposure; consider including other risk factors: second-hand smoke, family history of cancer, occupation and indoor/outdoor air pollution (the latter requires a harmonised approach).

5. Risk-based selection of eligible participants for study entry into lung cancer CT screening programmes (e.g. risk prediction modelling) would be advisable.

6. The current Chinese risk models (for either individual risk or nodule malignancy prediction) should be validated externally, especially in an ongoing lung cancer LDCT screening programme, which could help to confirm the efficacy and effectiveness in the real world. Further optimisation may be integrated over time, i.e. integration with liquid biomarkers and genetic factors.

7. Development of new risk prediction models, specifically for the Chinese population, should be priority, utilising optimal data sources.

8. Cost-effectiveness analysis of all current CT screening programmes should be undertaken, taking into consideration the selection criteria/risk threshold utilised, which would achieve the maximum net benefits over harms.

9. Evaluation of related parameters involved in the screening programmes requires further research in China, e.g. screening interval, screening length, nodule management.

10. Lung cancer screening programmes should be integrated with tobacco control strategies. An a priori design and a detailed record on participants' behaviours/perspectives and study costs including personnel cost, is required for cost-effectiveness evaluation.