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CT screening for lung cancer: Are we ready to implement in Europe?

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ABSTRACT

Lung cancer screening with low-dose CT (LDCT) is already available in certain parts of the world, such as the United States, but not yet in Europe. The recently published European position statement on lung cancer screening has recommended planning for implementation of screening to start within 18-months [1]. Pilot European programmes are already underway, primarily in the United Kingdom (UK), delivering lung cancer screening to their local populations. This review article acknowledges the evidence base for LDCT screening and will discuss the challenges that still need to be overcome in an attempt to answer the question: are we ready to implement in Europe?

1. European burden of lung cancer - the challenge for lung cancer screening

Lung cancer is the leading cause of cancer death in the world responsible for 1.6 million deaths per year [2]. This approximates to 20% of all cancer deaths globally, more than breast, colon and prostate cancers combined [3]. The burden of lung cancer is expected to rise across the globe in coming years despite advances in diagnostics and treatment [4]. This is largely due to a more recent peak in the tobacco epidemic in less developed countries and an overall aging population. Across Europe there are around 400,000 new cases of lung cancer and over 300,000 deaths annually [5]; some geographic variation exists with the highest incidence in men seen in Hungary and other central / eastern European countries, whereas the highest rates in women are in northern Europe in countries such as Denmark [5]. Long term survival remains poor, the average European 5-year survival is 12%, ranging from 5% in Bulgaria to 15% in Austria [6]. A significant factor driving poor outcomes is late presentation, with 70% of cases diagnosed at an advanced incurable stage and as a result as many as a third die within three months of diagnosis [7]. Although major therapeutic advances have been made in recent years with the introduction into routine clinical practice of targeted therapies and immunotherapies, only surgery has been demonstrated to improve long term survival [8]. A focus predominantly on improving therapy for those presenting with symptomatic disease rather than prevention and early detection would therefore be misguided. In England, 35% of lung cancers are diagnosed following emergency presentation and of these 90% are stage III or IV [9]. In contrast, 5-year survival in patients diagnosed early (stage I-II) can be as high as 75%, especially in patients who have a surgical resection [10]. It is therefore widely accepted that earlier diagnosis moves the focus from palliative treatment of incurable disease to radical potentially curative treatment with a resultant transformation of long-term survival.

2. The evolution of CT in lung cancer screening

Lung cancer screening dates back to the 1960s where technology was limited to sputum cytology and chest x-ray (CXR). A number of studies between the 1960s and 1980s were unable to demonstrate mortality benefit with either test [11–14]. The role of CT in the detection of lung cancer was first described in the 1990s and was shown to be superior to CXR in a number of subsequent observational studies [15–18]. In 2011, the National Lung Screening Trial (NLST) confirmed for the first time a significant mortality reduction in ever-smokers aged 55–74 years [19]. This trial is unique in that it recruited the required sample size to maintain 90% statistical power and demonstrate a mortality reduction from LDCT screening (90% power to detect a 21% difference in mortality). 53,454 individuals age 55–74 were randomised to receive either annual LDCT or CXR for three years if they had at least a 30 pack year smoking history and smoked within 15 years.

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Table 1
List of selected European lung cancer screening studies/pilots including eligibility and baseline results with NLST included for comparison.

Study (recruitment period)	Screening Methods (duration)	Number of participants Enrolled	Age eligibility criteria (years)	Smoking eligibility criteria	Baseline Cancer Detection Rate (%)	Proportion of Early Stage (I + II) Cancers (%)	Surgical Resection Rate (%)
DEPISCAN (2002-04)	Annual LDCT vs CXR (2 years)	765	50-75	≥15 PY; Ex-smokers quit within 15 years	2.4	37.5	Not stated
DANTE (2001-06)	Annual LDCT vs No Screen (4 years)	2,472	60-74	≥20 PY; Ex-smokers quit within 10 years	2.2	57.0	67.9
ITALUNG (2004-06)	Annual LDCT vs No Screen (4 years)	3,206	55-69	≥20 PY; Ex-smokers quit within 10 years	1.5	47.6	81.0
DLCST (2004-06)	Annual LDCT vs No Screen (5 years)	4,104	50-70	≥20 PY; Ex-smokers quit within 10 years	0.8	53.0	65.0
MILD (2005-11)	Annual LDCT vs Biennial LDCT vs No Screen (5 years)	4,479	≥49	≥20 PY; Ex-smoker quit within 10 years	0.8	63.0	84.0
LUSI (2007-11)	Annual LDCT vs No Screen (5 years)	4,052	50-69	At least: a) 15 CPD for 25 years OR b) 10 CPD for 30 years; Ex-smoker quit within 10 years	1.1	80.0	Not stated
UKLS (2011-2014)	Single LDCT vs No Screen (Single round)	4,055	50-75	$LLP_v2 \geq 5\%$	1.7	85.7	83.0
NELSON (2003-06)	LDCT at 1, 2, 4 & 6.5 years vs No Screen	15,822	50-75	At least: a) 15 CPD for 25 years OR b) 10 CPD for 30 years; Ex-smoker quit within 10 years	0.9	70.8	Not Stated
Manchester (2016-2018)	LDCT at baseline and 1 year	1,384	55-74	$PLCO_{m2012} \geq 1.51\%$	3.0	80.0	65.0
NLST (2002-2004)	*Annual LDCT vs CXR (3 years)*	*53,454*	*55-75*	*≥30 PY; Ex-smokers quit within 15 years*	*1.0*	*57.1*	*69.1*

PY = Pack years; LDCT = Low-dose computer tomography; CPD = Cigarettes per day; LLP = Liverpool Lung Project risk model;PLCOm2012 = Prostate, Lung, Colorectal and Ovarian trial risk model, the 2012 model; PanCan = Pan-Canadian study risk model.

The study demonstrated a relative reduction in lung cancer mortality of 20% and a 6.7% reduction in all-cause mortality in the LDCT arm. Since the publication of NLST, several American bodies, including the US Preventive Services Task Force (USPSTF), have recommended screening with LDCT be offered to individuals that match the NLST eligibility criteria extended to age 80 [20]. However, widespread implementation has been limited post-2011 due to the absence of a second confirmatory randomised controlled trial (RCT) despite the quality of evidence provided by NLST. In Europe, even though a number of smaller studies [21–28] (Table 1) have contributed to the literature further the results of the European Dutch-Belgian randomised lung cancer screening study NELSON were eagerly awaited. Although final publication of the peer-reviewed data are still awaited, the results were presented in a plenary session at the World Conference on Lung Cancer 2018 in Toronto, Canada in September 2018 [29]. The NELSON study was designed to detect a 20–25% lung cancer mortality reduction ten years after randomisation with a power of 80%, requiring 17,300-27,900 participants [30]. The trial under-recruited, randomising 15,792 participants, but despite this confirmed a 26% mortality rate reduction in males (95%CI 0.60-0.91, p = 0.003) and 39% in females (95%CI 0.35–1.04, p = 0.0543) at ten years [29]. At the same conference, the 10-year follow-up results of the MILD study were also presented which demonstrated a statistically significant 39% reduction in lung cancer mortality (0.59; 95%CI: 0.38-0.92) [31]. NLST and NELSON provide data from two large RCTs that LDCT screening is effective in reducing lung cancer mortality and given the scale of the lung cancer pandemic, LDCT screening can play an important role in reducing deaths from the disease.

3. How do we select the right population to screen?

Age is a validated independent risk factor for lung cancer and should be an important consideration in screening programmes yet the age inclusion criteria varies greatly between screening studies, ranging from 50 to 80. The combined median age of the largest observational studies (n = 13) is 59 years, significantly below the average age for lung cancer diagnosis [32]. Only 8.8% of participants in NLST were aged 70 or above. With the use of risk stratification models, age plays an important role in determining individual risk. This was demonstrated in UKLS where only 0.5% of those ages 50–55 were classified as high risk compared to 24.8% in those ages 71-75. Microsimulation models have suggested inclusion in screening programs should be extended beyond the age of 74, up to the age of 80 [33]. This has been reflected in the USPSTF criteria which includes those up to the age of 80. However, extending the upper age limit for eligibility can be associated with a lack of screening participation [34] and therefore making screening accessible to older participants provides additional challenges. Furthermore, extending screening to older age groups can increase the risk of overdiagnosis from competing co-morbidities [35], such as cardiovascular disease [36,37], but appears to be off-set by an

improved cost-efficiency of screening. Current recommendations appear to favour extending the upper age limit to age 80 years [20,38].

To date age and smoking history alone have been the basis for selection criteria in all but one RCT. Although both are clearly very significant, other well established risks for lung cancer are also important such as family history, socioeconomic status, occupational exposures, previous respiratory disease and previous cancer history (lung and non-lung cancers e.g. head & neck cancers). Increasing the precision of screening reduces harms and improves efficacy [39]. To address this issue several risk prediction models have been established, most of which have been shown to perform better than NLST criteria alone. Retrospective analysis of NLST by stratification into quintiles of 5-year risk of lung cancer death demonstrated that 88% of prevented deaths were in 60% of the highest risk participants whereas, conversely, the lowest risk quintile accounted for only 1% of prevented deaths [40]. The number needed to screen (NNS) to prevent one death in the highest risk quintile was 161 compared to 5,276 in the lowest risk quintile. Several risk models appear to be useful in this regard; the accuracy of these models will determine their utility and largely depend upon their calibration and discriminatory performance [41]. The Prostate, Lung, Colorectal and Ovarian (PLCO) risk model was derived using population data including non-smokers from the randomised PLCO trial [42]. A number of variables were used to calculate 6-year lung cancer risk including: age, socioeconomic status, BMI, ethnicity, sex, family history of lung cancer, personal history of cancer (both lung and non-lung) and respiratory disease as well as detailed smoking history. The performance of the $PLCO_{m2012}$ risk calculator, when compared retrospectively with NLST criteria for selecting participants at risk of lung cancer mortality, demonstrates better sensitivity, higher positive predictive value (PPV) without loss of specificity [43]. At a $PLCO_{m2012}$ threshold of $\geq 1.51\%$ lung cancer specific mortality rates in the NLST population were consistently lower in the LDCT arm and the NNS to prevent one lung cancer death reduced from 963 to 255 [44]. The recently published Pan-Canadian study, using a precursor to $PLCO_{m2012}$ at a threshold of 2% to select participants, diagnosed lung cancer in 5.1% of participants at baseline [45]. A recent UK NHS implementation pilot used the $PLCO_{m2012}$ model at the $\geq 1.51\%$ threshold and reported a lung cancer detection rate of 3% at baseline, higher than NLST, UKLS and NELSON [28] (Table 1). These are the first examples of lung cancer risk prediction models being prospectively used in real-world lung cancer screening implementation programmes. The Liverpool Lung Project (LLP_{v2}) model was developed using a case-control study and takes into account multiple variables including smoking, respiratory disease, asbestos exposure, previous cancer diagnosis and family history of lung cancer [46]. The LLP_{v2} model, at a threshold of $\geq 5\%$, was used in the only RCT to date to select participants based on lung cancer risk, and identified a higher prevalence of lung cancer than NLST at baseline. A number of other risk models have been developed [47–50] but there are currently no prospective comparative data to guide the selection of the most appropriate risk prediction tool. Two RCTs are in progress, the International Lung Screening Trial (ILST) [51] and the Yorkshire Lung Screening Trial (YLST) [52], that may clarify this in the years ahead. At present, modeling work has suggested that $PLCO_{m2012}$ performs best in external validation with the highest sensitivity, specificity and positive predictive values with modest superiority to the Bach and LLP models [53,54].

Selection of an appropriate risk threshold impacts on clinical performance of screening programmes but may also address challenges around implementation such as limiting the number of LDCT scans, non-invasive and invasive investigations and ultimately influencing costs and cost-effectiveness.

4. Lung cancer screening – ensuring engagement with the hard-to-reach

Of the many challenges for implementation, ensuring screening services are accessible to those at highest risk, and therefore most likely to benefit, is key. Demographic factors linked with lung cancer risk, for example current smoking and low socioeconomic status, are also associated with lower screening uptake [55,56]. Participation bias has been seen across the screening studies, including NLST and UKLS, where participants have been from more educated and affluent backgrounds [57,58]. Evidence points to 'practical barriers', such as travel, costs and a lack of willingness to attend hospitals, to be important reasons for non-participation [34]. One potential way to address travel obstacles and a fear or anxiety of clinical spaces is the use of community-based CT scanners at mobile or fixed sites. No study has directly compared mobile vs hospital-based screening in lung cancer however compliance in previous studies using mobile scanners has been good [59,60]. In a recent UK NHS pilot, a community-based lung cancer screening service used mobile CT scanners located in more deprived areas of the city and found demand for the service was high as were measures of deprivation (75% of participants in lowest quintile for deprivation), smoking (53% current smokers), educational achievement (82% left school by 16), lung cancer risk ($> 55\%$ had a $PLCO_{M2012}$ score $\geq 1.51\%$) and lung cancer detection (4.4% diagnosed with lung cancer over two rounds of screening) in those screened suggesting that community-based programmes facilitate enrichment for the target population and could be a key element of implementation [28,61]. 'Emotional barriers' including avoidance, fear and anxiety have also been shown to contribute to a lack of engagement with screening programmes [34] and may also be addressed by this approach. Additionally, the use of 'Lung Health Checks' which are discussed in more detail later in this review may further ameliorate the psychological barriers that 'lung cancer screening' may generate.

Improving uptake of screening amongst those at highest risk is essential and critical for implementation [62,63]. Details of the methods of recruitment, public engagement, involvement of primary care physicians and other community health services has varied in the European screening studies and achieved mixed results (Table 2). In the United States, uptake of lung cancer screening has been poor with only an estimated 3.9% of potential participants receiving LDCT screening in 2015 [64]. The reasons for this are likely to be multifactorial and yet to be fully understood. Organisational barriers, which include engagement, communication, screening site, insurance coverage and reliance on primary care physicians to opportunistically identify and refer potential participants may all contribute to poor uptake.

5. Optimum screening model

The optimal model of screening and most effective relationship between commissioner, primary care and provider is not yet established but will clearly be influenced by prevailing healthcare systems in individual countries. Several models are described including centralised, decentralised and hybrid models [65] (Fig. 1). Decentralised models favour implementation based on primary care assessment and referral, with or without engagement programmes, to diagnostic providers. This model may be disadvantaged by a lack of uniformity in risk assessment, radiology interpretation and nodule management (with implications for cost, false positives and overdiagnosis) and does not afford providers a clear opportunity to invest in the required capacity to deliver a new service. Quality assurance is also more difficult to monitor from recruitment to treatment. Centralised models are driven by the provider creating capacity and encouraging primary care referral but are disadvantaged by a lack of comprehensive community or primary care engagement. Referral rates may therefore be low but quality assurance more easily maintained. Whether centralised models should be confined to cardiothoracic surgical centres or utilise general hospitals is also not well understood but clear agreement exists that accreditation is required based on the facilities, expertise and capacity to provide a high quality programme. Hybrid models typically work in collaboration, providing a clear strategy for community and primary care education

Table 2
Recruitment methods, primary care involvement and response rates in selected European lung cancer screening studies/pilots with NLST included for comparison.

Study	Recruitments approach	PCP involvement	Response rate (%)
DEPISCAN	PCPs & physicians approached and asked to opportunistically enroll individuals matching selection criteria	Yes	830 (% not stated)
DANTE	Generalised advertising through mass mailings, leaflets and local media	Yes	2,564 (% not stated)
ITALUNG	PCP endorsed invitation letters to pre-identified individuals	Yes	23.9
DLCST	Advertisement in newsprints	No	4,104 (% not stated)
MILD	Advertisement in newsprints and television	No	4,099 (% not stated)
LUSI	Population based invitation letters + 'mass media' information release	No	32.7
UKLS	Mass invitation letters sent to pre-identified individuals	Yes	30.7
NELSON	Mass invitation letters to candidates identified through population registries	No	32.0
Manchester	PCP endorsed invitation letters to pre-selected populations; 'mass media' promotion; Outreach through community networks, events and awareness sessions	Yes	28.5*
NLST	*Generalised advertising through mass mailings, leaflets and local media; Outreach including health fairs and presentations to unions and community groups; Web sites, Internet-based, television and radio announcements.*	*No*	*53,454 (% not stated)*

PCP = primary care physicians; *Maximum service capacity reached.

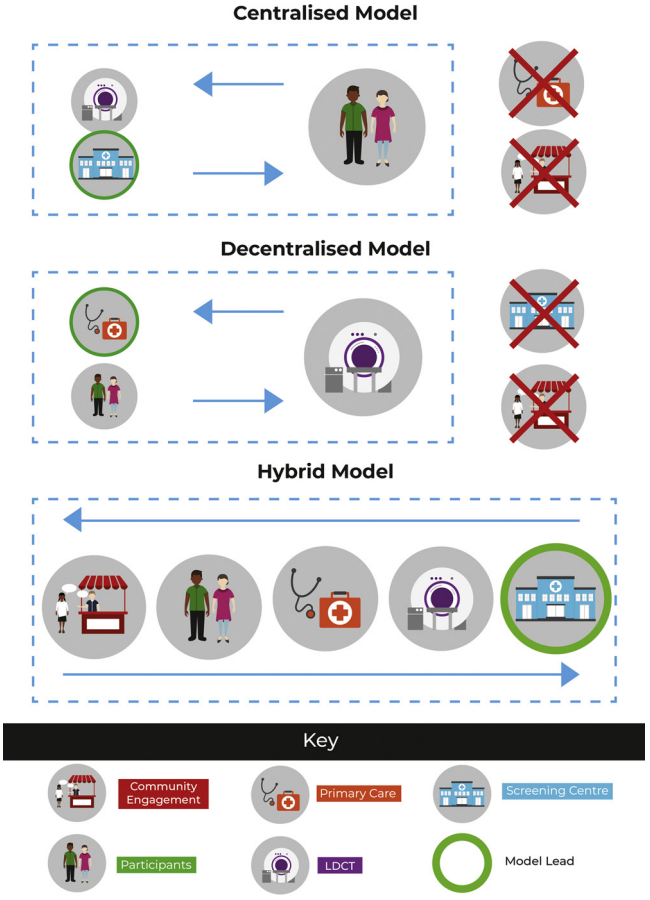

Fig. 1. Graphical description of different screening models and the key components involved.

and engagement, and full responsibility for delivery of recruitment, assessment, diagnostics and treatment lying with the provider. This has the advantage of being a single system to facilitate quality assurance and monitoring of key performance indicators overseen by an inclusive stakeholder committee. It seems reasonable that implementation programmes should not simply focus on the act of referral and CT screening but ensure robust plans for targeting those at highest risk, describe a comprehensive community engagement plan to reflect local community differences, such as public transport, ethnicity and language, and a collaborative partnership with public health, commissioning, primary care stakeholders and providers of diagnostics and treatment.

The recent American Thoracic Society (ATS) guide to implementation describes 16 example lung cancer screening programmes, the majority of which are centralised or hybrid models suggesting perhaps that decentralised models are less favourable [65]. The successes of NLST, UKLS and NELSON also favour a centralised model noting the challenges of attracting the most at risk. The recent UK Manchester pilot is a hybrid model utilising commissioner-cardiothoracic centre collaboration, an effective community engagement team (responsible to the commissioner) with full contractual responsibility for delivery and quality assurance resting with the cardiothoracic centre. The encouraging results of this pilot, noting the difficulties in implementing screening in the US, suggest that hybrid models, particularly based in cardiothoracic centres, merit primary consideration in implementing lung cancer screening programmes across Europe.

6. Lung cancer screening or lung health check?

Lung cancer screening is known to elicit emotional barriers to screening uptake [34]. A novel approach that may overcome or minimise this is to promote a 'Lung Health Check' (LHC) of which lung cancer screening is a part, as demonstrated in recent implementation pilots and research studies in the UK [28,66]. This approach, which downplays 'cancer screening', is seen as less intimidating and is less likely to illicit the previously described emotional barriers to screening [67]. This not only has the potential to improve screening uptake but also provides an opportunity to address tobacco addiction and competing causes of premature death such as cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) [68]. With a LHC approach, ever-smokers may be invited for an assessment that can include spirometry, CVD risk assessment and treatment and support for tobacco addiction. Incorporation of a lung cancer risk model is key, with those exceeding an agreed risk threshold proceeding to LDCT screening directly. Successfully combining effective smoking cessation with lung cancer screening has the potential to increase the mortality reduction from screening [69,70]. For example, modeling work in the United States has suggested that a 10% quite rate within a screening programme with 40% uptake could lead to 160,000 fewer lung cancer deaths and 1.4 million life years gained by 2060 [71]. Evidence for successful smoking cessation across lung cancer screening trials have been mixed [72,73] although previous concerns regarding false

reassurance after a negative screening scan have been largely unfounded and recent evidence from UKLS suggest LDCT screening is associated with improved smoking cessation rates [74]. This effect could be improved further by incorporating pharmacotherapy, which has been shown to increase successful cessation rates by threefold compared to placebo [75].

Performing spirometry in such a high-risk population of current or former smokers has the potential to identify previously undiagnosed symptomatic COPD. The burden of undiagnosed COPD, which is associated with increased risk of exacerbations, pneumonia and death [76,77], is substantial and has a significant clinical and economic impact on health systems [78,79]. The similarities between risk factors for both lung cancer development and 10-year risk of CVD highlights an opportunity to address unrecognised cardiovascular risk in a lung cancer screened population. It is noteworthy that CVD was the leading cause of death in the NLST population [37] and modification of CV risk provides an evidence-based opportunity to minimise overdiagnosis. This can be done either non-radiologically through CVD risk prediction models, such as QRISK [80] or Framingham [81], where an evidence base exists for pursuing statin therapy [82], or through the detection of coronary artery calcification (CAC) on LDCT which is strongly correlated with cardiovascular events and all-cause mortality although it remains unclear how best to approach this entity [83,84]. A UK pilot study identified a third of lung cancer screening participants as at high risk of CVD using the QRISK2 model but not prescribed primary prevention as recommended by national guidelines [36].

Judicious identification of cardiorespiratory disease and comprehensive approaches to tobacco addiction within the context of lung cancer screening programmes has the potential for additional benefit rather than harm, and may further contribute to the cost-effectiveness of screening [85].

7. Ensuring harm reduction through evidence based algorithms

There is a risk, as with any screening programme, of harm to participants despite careful evaluation. In CT screening for lung cancer, the well-established concerns relate to 1) overdiagnosis, 2) radiation-induced lung cancers, 3) false positive screens and subsequently 4) investigation of benign disease including benign surgical resection rates.

7.1. Overdiagnosis

This is the diagnosis of disease that would never be clinically relevant within the participants expected lifetime i.e. death due to competing causes. In tumours with low volume doubling times (VDT), addressing the competing causes of death affords an opportunity to improve lung cancer mortality and 5-year survival. However, diagnosis and treatment of indolent lung cancers should be avoided and represents the major burden of overdiagnosis. The rate of overdiagnosis can be estimated within randomised controlled trials by the number of excess cancers in the screening arm compared to the control arm. In other words both arms should have the same number of relevant cancers. The estimated rate of overdiagnosis amongst screening trials has varied significantly, ranging from none in the ITALUNG study to 67% in DLCST [86,87]. The overdiagnosis rate in NLST is estimated at 18% but the follow-up period was short at 6.5 years [19] with subsequent modelling suggesting that this overdiagnosis rate is likely to be overestimated. The majority (80%) of overdiagnosed cancers were regarded as bronchioloalveolar carcinoma (BAC), an entity now regarded as adenocarcinoma in-situ easily recognised on CT, associated with an excellent cancer-specific prognosis and managed conservatively [88]. The same modelling suggests in the event of lifetime follow-up in NLST the estimated non-BAC overdiagnosis rate was less than 5% [89]. Through adherence to modern nodule management protocols and the principles of the 8th edition of the TNM staging manual [90], overdiagnosis can be reduced significantly ensuring the minimisation of harm. To support this, the ITALUNG investigators recently reported a low rate of overdiagnosis over an adequate follow up period [87]. Furthermore, models examining the effectiveness of screening strategies confirm that lung cancer screening may prevent between 3 and 5 lung cancer deaths, depending on the stopping age of the screening program, for every overdiagnosed case. This is in sharp contrast to prostate or breast cancer screening where cancer deaths prevented are estimated at 1 per 5 or 3 overdiagnosed cases respectively [35]. We would argue that this risk of overdiagnosis within quality assured programmes, when weighed against the mortality and societal burden of this disease, is insufficient to limit the implementation of lung cancer screening. Additional strategies to reduce death from competing causes (thereby reducing the likelihood of death following curative treatment of invasive malignancy) may help to further reduce overdiagnosis.

7.2. Radiation

CT scanning exposes a participant to radiation and a risk of radiation induced cancers. The American College of Radiology (ACR) practice parameter for the performance of imaging in lung cancer screening recommend low-dose CT scanning set to yield a volume CT dose index (CTDIvol) of < 3 mGy for a standard-sized patient, modified according to body size [91]. Exposure from repeated scanning and further investigations, such as PET-CT and CT guided biopsies, as a result of screening are a potential concern. Bach et al estimated approximately one radiation induced cancer death from every 2,500 NLST screens [92]. Rintoul and colleagues estimated the mean lifetime attributable risk of malignancy for those receiving curative intent treatment as 0.059% with a lung cancer specific risk of 0.019% [93]. Rampinelli and colleagues estimated 1.5 radiation induced lung cancers and 2.4 other major cancers after 42,000 LDCT scans over ten years (that included cumulative radiation exposure from diagnostic CT and PET-CT scans) [94]. Consequently, the evidence supports a very low risk of radiation induced malignancy that can be further reduced by the implementation of ultra-low dose CT scanning, achieving a dose one-tenth of the conventional LDCT [95]. When weighed against the potential benefit, the evidence to date would suggest the life years gained from LDCT screening of high-risk populations outweighs the estimable risks from radiation exposure.

7.3. False positives and investigation of benign disease

The principal role of LDCT is to detect pulmonary nodules. The vast majority are small (less than 5 mm), benign, and their morphology is variable. Consequently, this provides challenges in evaluation and diagnostic interpretation and influences the rates of both positive and interval scans and ultimately has implications for false positive rates. Defining what constitutes a positive scan is important as this affects assessment capacity, costs and causes short term anxiety and stress for participants [96,97]. Variable definitions of a 'positive' scan, based on linear size or nodule volume, affect both positivity and false positivity rates across the lung cancer screening literature (Table 3). Clearly, higher positive rates have implications for rates of radiation exposure, non-invasive and invasive investigations, benign surgical resections and psychological harm. To mitigate against high referrals and false positive rates in particular, implementation will require use of volumetric analysis [98], robust nodule management protocols [99,100], including nodule risk stratification models [101], and in the near future incorporation of artificial intelligence (AI) algorithms. Such approaches can reduce scan positivity rates, false positivity rates and improve performance indices (sensitivity, specificity, negative predictive value) [61,102]. Another important question to address is how often to screen participants once selected as high risk. To date, only one study (MILD) has directly compared annual vs biennial LDCT and found no significant difference in recall rates, prevalence or incidence cancer diagnosis [103]. The NELSON group have demonstrated an interval of 2.5 years is

Table 3
Details of positive and false positive definitions from the baseline results of selected European lung cancer screening studies/pilots with NLST included for comparison.

Study	Definition of a positive result	Definition of a false positive result	Reporting radiologists (as defined by authors)	Scan positivity rate (%)	False positive rate* (%)	Benign resection rate (%)
DANTE	NCN ≥ 10 mm or smaller but showing spiculated, focal GGOs, major atelectasis, endobronchial lesions, mediastinal adenopathy, pleural effusion or pleural masses	Any positive CT result with no final diagnosis of lung cancer	Experienced chest radiologists	15.6	14.5	18.8
ITALUNG	NCN ≥5 mm; NSN ≥10 mm; Any part-solid nodule	Any positive CT result with no final diagnosis of lung cancer	Radiologists with a minimum of 4 years' experience in chest CT	30.3	28.8	5.5
DLCST	All nodules ≥5 mm and all growing nodules	Any positive CT result with no final diagnosis of lung cancer	Board certified radiologists	8.7	7.9	18.2
MILD	All nodules ≥5 mm and all growing nodules	Any positive CT result with no final diagnosis of lung cancer	Trained radiologists	15.0 (annual) 14.0 (biennial)	12.0	9.0
LUSI	All nodules ≥5 mm and all growing nodules	Any positive CT result with no final diagnosis of lung cancer	Especially trained radiologists	26.6	25.5	29.6
UKLS	Nodules greater than 500 mm3 or 10 mm maximum diameter at baseline and nodules that demonstrated growth on follow-up CT (VDT < 400days)	Those requiring further diagnostic investigation more immediately than a repeat scan, but who subsequently did not have lung cancer.	Experienced thoracic radiologists	5.7	3.6	10.3
NELSON	Nodules greater than 500 mm3 or 10 mm maximum diameter at baseline and nodules that demonstrated growth on follow-up CT (VDT < 400days)	Those requiring further diagnostic investigation more immediately than a repeat scan, but who subsequently did not have lung cancer.	Not specified	6.0	3.6	Not stated
Manchester	Nodules ≥8 mm with BROCK score ≥10% at baseline or nodules that demonstrated growth on follow-up CT (VDT < 400days)	Those requiring further diagnostic investigation more immediately than a repeat scan, but who subsequently did not have lung cancer.	Experienced thoracic radiologists	5.9	2.8	0.0
NLST	*All non-calcified nodules ≥4mm*	*Any positive CT result with no final diagnosis of lung cancer*	Especially trained radiologists	*24.2*	*23.3*	*24.4*

NCN = non-calcified nodule; NSN = non-solid nodule; GGO = ground-glass opacities; VDT = volume doubling time.
* As a proportion of entire screened population.

potentially harmful with a higher rate of interval cancers when compared to 1-year and 2-year intervals and the majority of interval cancers occurred in the final six months of the 2.5 year interval [104]. There was no statistically significant difference between the 1-year and 2-year interval groups. The evidence therefore suggests going beyond two years for interval imaging is detrimental. Microsimulation models and data modelling equations have shown mixed conclusions regarding annual vs biennial screening [105]. The best approach is likely to depend on risk stratification of individuals and tailoring frequency of screening based on this, as is done in breast cancer screening [106]. The results of an individual's baseline screening LDCT could be used to further determine frequency of subsequent screening as the presence of no nodules on the baseline screening scan is associated with reduced risk of subsequent malignancy [107]. However, in recent real-world data from a screening pilot cancers that developed in individuals with true negative baseline scans had mean VDT of 49 days suggestive of a more aggressive phenotype that would be unsuited to biennial screening and support the argument for annual screening [61]. Data from NELSON has also demonstrated new nodules detected on incidence screening have a higher risk of malignancy than those detected at baseline and therefore smaller size criteria are recommended for investigation of new nodules on incidence screening rounds [108].

8. What is the key infrastructure required for successful implementation?

Full scale implementation of lung cancer screening across whole populations will be a significant challenge and remain so even if a more targeted approach is taken. Ensuring that the right participant has convenient access to a high quality programme will require consideration of engagement strategies, the service model (discussed previously), CT resource, reporting capacity and quality assurance, and the impacts on diagnostic and treatment providers. The widespread adoption of volumetry, computer aided detection (CAD) and ultimately AI has the potential to reduce reporting times in the short term but will attract additional training needs and may include the use of CT-reporting radiographers. Quality assurance such as that seen in breast cancer screening programmes also needs to be developed and addressed [109]. Many parts of Europe are in crisis in relation to radiology capacity [110]; implementation in the medium-long term will require multifaceted strategies including enhanced training, networked reporting and an expansion of a high quality workforce [111].

The optimal model of care for screening is yet to be determined, but centralised or hybrid models appear most abundant in the published literature. Commissioning specialist cardiothoracic centres has several advantages that are less likely to be available to other models. As regional providers of current care for suspected lung cancer, a broad range of sub-specialty expertise in pulmonology, thoracic radiology, nodule management and thoracic surgery is likely to already exist and include skills in interventional pulmonology, navigational bronchoscopy, sub-centimetre CT-guided biopsy and minimally invasive surgery. Any uplift in infrastructure required from the additional referrals of a screening programme are likely to be relatively small compared to non-specialist centres. The use of a single provider, as opposed to a distributed model, facilitates program consistency, robust delivery of agreed service specifications [112], quality assurance, cost-effectiveness, reinvestment and enables hospital executives to effect the necessary operational and managerial changes required for an accredited service. National registries will facilitate monitoring of designated centres and the rapid integration of new learning and screening standards. Whilst implementation based across smaller non-specialist hospitals is also possible, care must be taken to avoid variability in some clinical outcomes as previously seen in national audits [113], including surgical resection rates [114,115].

9. An example of the estimated impact of population screening using a hybrid model incorporating a lung health check approach

The recent UK pilot of NHS implementation [28] provided important data in a real life setting to estimate the impact of a centralised roll-out of community based CT screening within a Lung Health Check programme across a geographic population of 3.2million in the north-west of England. Using population figures from 10 clinical commissioning groups, there is an estimated 627,000 potential participants aged 55-80. Ever-smokers represent 59% of the population (n = 372,000). Assuming a 50% uptake for screening and eligibility for LDCT at $PLCO_{m2012} \geq 1.51\%$, a comprehensive programme would require over 90,000 CT scans annually, leading to more than 5,300 referrals for assessment, and > 2,760 new lung cancers diagnosed, nearly 80% at stage I/II. In the first year of screening alone, one could expect over 1,900 lung resections, a four-fold increase over existing levels of activity. Planning for such activity clearly requires significant investment in equipment, estate and personnel at diagnostic and treatment centres. It is highly likely that the chosen model of care would impact on deliverability and financial sustainability.

10. Conclusion

Results from two randomised controlled trials confirming a mortality reduction from low-dose CT screening argues for implementation of lung cancer screening. Real world implementation pilots in the UK demonstrate this to be feasible, attracting participants from hard-to-reach areas, attaining high rates of early stage lung cancer fit for curative treatment with low levels of harm (false positives, benign resection rates, radiation exposure). The adoption of volumetry and computer aided detection are necessary in the short term to minimise the impact on a resource limited radiology workforce and mobile ultra-low-dose CT technology and hybrid programs limit the impact on the resources of the broader healthcare economy whilst maintaining quality. There is an increasing recognition of the relevance of other cardiorespiratory disease in reducing all-cause mortality and potential overdiagnosis and the utility of Lung Health Check programmes as distinct from lung cancer screening.

So are we ready to implement lung cancer screening in Europe? This will depend on the approach taken for delivery. It is clear that the resources required for high quality programmes are limited and most likely, though not exclusively, concentrated in specialist centres. It is in our opinion that centralised or hybrid models of care involving specialist cardiothoracic centres with engaged senior management seem best placed to overcome the challenges to systematically manage and minimise harms and afford an opportunity to reinvest income from provided services to ensure capacity, sustainability and training.

Conflict of interest

We have no conflicts of interest to declare as a collective group regarding this particular work.

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