Early Diagnosis and Lung Cancer Screening

Haval Balata[1+2#], Samantha L Quaife[3], Christopher Craig[1], Daniel J Ryan[4],

Patrick Bradley[1+2], Philip J Crosbie[1+2], Rachael Murray[5], Matthew Evison[1]

[1]Manchester Thoracic Oncology Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK. [2]Division of Infection, Immunity and Respiratory Medicine, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK. [3]Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK. [4]Department of Respiratory Medicine, Beaumont Hospital, Dublin, Ireland. [5]Academic Unit of Population and Lifespan Sciences, Faculty of Medicine & Health Sciences, University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham, UK.

[#]**Corresponding author**: Dr Haval Balata, Manchester Thoracic Oncology Centre, Manchester University NHS Foundation Trust, Southmoor Road, Wythenshawe, M23 9LT. Tel +44 (0)161 291 3597. E-mail: haval.balata@mft.nhs.uk

Introduction

Lung cancer is responsible for nearly two million deaths across the world every year[1]. This is the single biggest cause of cancer death and accounts for approximately 20% of all cancer-related deaths. Lung cancer survival is driven by the stage at presentation. In the United Kingdom (UK), 57% of patients with stage I lung cancer, where curative-intent treatment can be considered, survive for five years or more. This compares to only 3% of patients with stage IV lung cancer, where treatment is palliative[2]. In 2020, 44% of patients with lung cancer in England presented at stage IV disease, compared to 20% at stage I and 28% at stages I-II combined[3]. Therefore, a key ambition in the strategy for improving outcomes in lung cancer is earlier diagnosis and the National Health Service (NHS) 'Long Term Plan' has set a target to diagnose 75% of all cancers at stage I-II by the year 2028[4].

Earlier diagnosis of symptomatic lung cancer

Lung cancer can present with no symptoms, lung-specific symptoms (haemoptysis, cough, breathlessness and chest pain) and non-specific symptoms (weight loss, fatigue, loss of appetite). Many of these symptoms are exceptionally common with a very broad range of alternative diagnoses, providing a diagnostic challenge for clinicians. There are, therefore, barriers at both a public level, in how to interpret and mange such symptoms, and at healthcare professional level, in when to perform further investigation such as a chest-X-ray (CXR) and when to refer to hospital on a suspected lung cancer pathway. Public insight research in the North of England identified that a lack of validation of symptoms that could be caused by lung cancer, previous experiences in seeking healthcare professional review, an underestimation of the potential risk of lung cancer and a lack of prioritisation of an individual's symptoms in the context of an over-stretched health care service can all act as barriers for the public to seek help with symptoms that could be caused by lung cancer[5]. Similar challenges face community-based clinicians in when to investigate or refer to hospital when symptoms could be caused by lung cancer. Almost one in three (30%) of patients with lung cancer have had three

or more consultations with their primary care physician before they are referred on the suspected lung cancer pathway suggesting an opportunity for earlier diagnosis[6]. One pivotal goal in the earlier diagnosis of symptomatic lung cancer is to increase access and uptake to CXRs for patients with persistent symptoms (lasting greater than 3 weeks) that could be caused by lung cancer. In a large city in the North of England, a dedicated public awareness campaign encouraging the public to have a CXR if they had cough, breathlessness or chest pain lasting 3 weeks or more (and offered a direct access pathway without seeing a community physician) increased the volume of chest x-rays by over 80%[7]. This was followed by a subsequent 8.8% increase in patients diagnosed at stage I-II (26.5% pre-campaign, 35.3% during campaign) and 9.3% reduction in the absolute number of patients diagnosed with stage IV lung cancer (1,254 pre-campaign, 1,137 during campaign)[7]. Whilst CXRs are an important tool in the diagnosis of lung cancer, 20-25% of patients with lung cancer will still have a normal CXR[8]. There is, therefore, important healthcare professional education and safety netting systems required to ensure that false reassurance is not provided by a normal CXR and patients in whom the suspicion of lung cancer persists should still be referred on the suspected cancer pathway. Furthermore, increasing the number suspected lung cancer referrals from primary to secondary care is associated with improved survival and earlier diagnosis of lung cancer. A national cohort study of 1.4 million patients in the UK demonstrated a reduced risk of death from lung cancer in patients from GP practices with a high referral rate on the suspected cancer pathway (HR 0.95, 95%CI 0.94-0.97)[9]. In summary, public awareness campaigns, healthcare professional education and clinical pathways that increase presentation in primary care, increase CXR uptake and increase suspected lung cancer referrals for patients with persistent symptoms that could be caused by lung cancer are the key priorities to improve the earlier diagnosis of symptomatic lung cancer in the UK.

Low-dose CT screening for asymptomatic lung cancer - summary of key RCTs

Screening for asymptomatic lung cancer began in the 1960s but was limited to assessing the roles of sputum cytology and CXR. Despite the increased incidence and resections rates of lung cancers in several randomised controlled trials (RCTs), none were able to demonstrate a mortality reduction[10-14]. In the 1990s, the role of low-dose computed tomography (LDCT) for detecting lung lesions was gaining traction and led to direct comparisons with CXR, eventually being proven to be superior at detecting early stage lung cancer in several studies, including the Early Lung Cancer Action (ELCAP) project[15-17]. These study results reignited an interest in lung cancer screening, this time examining the potential role of LDCT.

In 2011, publication of The National Lung Screening Trial (NLST)[18] was a breakthrough moment for lung cancer screening. This large American-based study randomised 53,454 participants, aged 55-74 with at least a 30 pack year smoking history and smoked within 15 years, to annual LDCT or CXR. Early stage lung cancer detection was significantly increased by LDCT and, more significantly, a 20% (95% CI 6.8-26.7; p=0.004) reduction in lung cancer mortality was demonstrated. Additionally, the results also demonstrated a 6.7% (95% CI 1.2-13.6; p=0.02) reduction in all-cause mortality. Since the publication of NLST, the US Preventive Services Task Force (USPSTF) have recommended screening with LDCT be offered to individuals matching NLST criteria, extended to age 80[19].

Since then, several smaller European studies (**Table 1**) have further demonstrated LDCT screening's ability to create a stage shift towards earlier detection of lung cancer but without the statistical power to further demonstrate mortality reductions. This was until publication of the Dutch-Belgian NELSON study in 2020, the second largest lung cancer screening RCT to ever be conducted, which was also powered to demonstrate mortality reduction[20]. Participants aged 50-75, with a smoking history of either ≥15 cigarettes for 25 years or ≥10 cigarettes for 30 years, were randomised to either LDCT screening at baseline, 1 year, 3 years and 5.5 years or no screening. At 10-years, lung cancer related mortality was reduced by 24% (0.76; 95% CI 0.61-0.94, 0=0.01) in the LDCT arm overall, with a more

significant mortality reduction in female participants (0.67; 95% CI 0.38-1.14). The trial was not powered to look at overall mortality. Additionally, the Multicentric Italian Lung Detection (MILD) trial, comparing annual LDCT, biennial LDCT (every 24 months) and no screening in participants aged ≥49 years with at least a 20 pack years smoking history, has also now demonstrated a statistically significant reduction in lung cancer mortality of 39% (0.61; 95%CI: 0.39-0.95) after 10 years of follow-up[21].

Real world outcomes from lung cancer screening implementation programmes in the UK

More recently, focus has shifted from RCTs demonstrating mortality reductions to smaller-scale studies demonstrating implementation. This has been primarily led by UK-based programmes over the past six years. Adopting a 'Lung Health Check 'approach, whereby participants from higher risk and more deprived geographical locations are invited to a face-to-face lung health check (or equivalent) and those at high risk of lung cancer, determined prospectively through the use of risk-prediction models, are selected for real-world LDCT lung cancer screening.

The Manchester Lung Health Checks, first piloted in 2016 using community-based mobile scanners, demonstrated a lung cancer detection rate of 4.4% across two annual screening rounds (3% at baseline and 1.6% at one-year) through offering LDCT screening to those with a $PLCO_{m2012}$ score of ≥1.51%[22,23]. Overall, 80% of screen detected cancers were diagnosed at an early stage (I-II), demonstrating an almost 5-fold reduction in stage IV disease compared with age-equivalent lung cancer diagnosis across Manchester. In the end, 89% of patient diagnosed with cancer received curative intent treatment with a surgical resection rate of 60%[22,23]. Similarly, the 'Liverpool Healthy Lung Project', published in 2019[24], reported a lung cancer detection rate of 1.9% through offering LDCT screening to those with a LLP_{v2} (Liverpool Lung Project) risk score of ≥5.0%, with 76% being diagnosed at stages I-II. The smaller West London screening pilot, which offered options of both mobile community-based scanners and fixed

hospital scanners participants with a $PLCO_{m2012}$ score of ≥1.51% or LLP_{v2} ≥2.0%, reported a lung cancer detection rate of 2.5%, with 58.6% diagnosed at stage I[25].

The London-based Lung Screen Uptake Trial (LSUT) was a RCT investigating whether uptake of screening can be improved with targeted invitation strategies[26]. Whilst the primary aim of the study was negative and showed no improvement in uptake through the use of targeted invitation leaflets, overall uptake was significant at 52.6%, again the majority with high socioeconomic deprivation. Participants with any of $PLCO_{m2012}$ ≥1.51%, LLP_{v2} ≥2.5% or ≥30 pack-years and smoked within 15 years (i.e. NLST criteria) were offered LDCT screening. Lung cancer prevalence was 4.7% in one baseline round, with 72.2% of cancers detected at an early stage and 79.4% offered radical curative-intent treatment[27].

These UK-based programmes have successfully demonstrated that a Lung Health Check approach to screening is acceptable to local participants and have been able to successfully engage highly deprived populations, previously missed in research trials, with the vast majority of participants being from the lowest deprivation quintiles in the UK. The programmes have all been able to detect significant numbers of early stage lung cancers amenable to radical treatment.

Optimising the uptake of lung cancer screening

Almost a decade since the USPSTF's recommendation, utilisation of lung cancer screening remains universally low across the United States (US) at 19% ever participation[28], of which an estimated 55% return for subsequent screening rounds[29]. The picture in the UK is relatively improved. Despite no national recommendations, the previously mentioned targeted programmes which offer screening within a Lung Health Check approach report between 21-53% first-time participation[22,25,27], with as much 90% attending the second screen[23]. However, to be equitable and maximally effective, screening programmes must do more to improve overall participation and they must also achieve a high-risk participant profile, yet participation has often been skewed in the opposite direction. Those

at highest risk of lung cancer are overrepresented within communities experiencing socioeconomic deprivation, where smoking prevalence is highest. Both socioeconomic deprivation and current smoking status have consistently predicted lower participation internationally[18,30-32], including for repeat participation[29]. In the US, disparities have also been observed for ethnicity, with lower participation by those from black ethnic backgrounds, among whom lung cancer incidence and mortality is already higher[33]. Screening programmes for other cancer types also warn of inequalities in participation by factors understudied in this context, such as rurality, comorbidities, and learning difficulties.

Achieving equality in participation needs evidence-based interventions that overcome barriers to participation while also supporting participation *and* non-participation as voluntary, informed choices. Research evidencing the determinants of inequalities in participation should direct targeted intervention design, from which the findings to-date can be organised within the framework of the Integrated Screening Action Model[34]. This includes motivational factors (e.g., low perceived efficacy of lung cancer screening/treatment, worry about high perceived risk of lung cancer[35-37]) as well as environmental and social factors affecting an individual's opportunity and capability to take part (e.g., perceived stigma, travel difficulties, comorbidities)[38,39]. In the LSUT, invitation materials with stepped, low burden and targeted content designed to address motivational factors helped reduce the socioeconomic gradient in participation[27]. Both arms included strategies for supporting capability and opportunity known to be effective for lower socioeconomic groups in other cancer screening contexts (i.e., advanced notification, reminder, timed appointment)[40]; together achieving 53% attendance across trial arms. While promising, inequalities persisted, and a substantial proportion of the invited population remained unengaged. In line with proportionate universalism, greater resource, innovation, and community engagement need to be invested to engage non-responders. The American Thoracic Society (ATS) recently recommended pathway navigation as one such promising approach[41], investing additional support for those facing greater difficulty in considering and participating in lung cancer screening.

Treating tobacco dependency in lung cancer screening programmes

Implementing smoking cessation interventions is likely to improve the overall effectiveness and cost effectiveness of screening programmes[42]. Individuals eligible for lung cancer screening believe the offer of smoking cessation support is acceptable and expected as part of the lung cancer screening process[43-45], and attendance at screening may provide a "teachable moment"; an opportunity to inform participants of the harmful effects of smoking at a time where they may be receptive to change their behaviour [46-48]. Indeed, an invitation to or attendance at lung cancer screening has been shown to increase motivation for quitting and quit rates in comparison to control groups[49,50]. A recent review of smoking cessation interventions in lung cancer screening reported baseline smoking cessation rates of between 7%-23% amongst smokers participating in research studies, regardless of intervention. Those receiving abnormal scan results appear to be particularly likely to quit smoking following engagement with lung cancer screening, with numerous studies reporting higher quit rates following an abnormal scan result or referral to a physician as compared to a normal scan result[51-54]. It has also been suggested that the provision of personalised information regarding the impact of smoking on their health may encourage uptake of lung cancer screening in those potential participants who smoke[45].

Given quit attempts are more likely to be successful if made with evidence-based support, attendance at lung cancer screening should be accompanied by an offer of an effective intervention. A systematic review synthesizing evidence regarding smoking cessation interventions in LDCT screening reported that there was insufficient data to suggest a particular approach to smoking cessation in the lung cancer screening setting[55]. Since this review was published, studies from countries including the UK, US, Canada, Italy, Netherlands and Belgium have investigated the efficacy of smoking cessation interventions in the LCS setting, with evidence of a greater impact of more intensive interventions (for example behavioural counselling and pharmacotherapies) compared to low intensity interventions (for example brief advice, self-help and internet materials). A UK based study has shown a high uptake

of an opt-out smoking cessation service offered to all smokers, co-located within a lung cancer screening programme[56]. The study is also testing the efficacy of adding a personalized intervention comprising the use of heart and lung images captured during the LDCT scan, highlighting areas of coronary artery calcification and emphysema, as part of the smoking cessation intervention[56]. Research in this area is continuing, however, with the US SCALE (Smoking Cessation within the Context of Lung Cancer Screening) collaboration testing various permutations of smoking cessation intervention strategy and intensity with a core of data collection measures to allow meaningful comparisons[57].

The effects of smoking cessation extend beyond lung cancer. People who smoke are also at risk of premature death due to chronic obstructive pulmonary disease (COPD), heart disease and stroke. Subjects eligible for lung cancer screening have a three times greater relative risk death due to heart disease than a non-smoker[58] and participants in lung cancer screening studies have shown notable proportions of coronary artery calcification and emphysema[59-61]. There is thus a potential opportunity to provide better management and reduce the clinical impact of these conditions through effective smoking cessation intervention delivered as part of lung cancer screening, building on the teachable moment in those attending for screening.

Minimising harm from lung cancer screening

Any form of screening has the potential to cause harm if not performed in a safe and quality assured manner. In lung cancer screening, unnecessary radiation, overdiagnosis and actions related to false positive findings are the most significant harms that need considered. The evidence base for lung cancer screening is based on the use of LDCT, which is 70-90% less than a standard CT Thorax (1.5-mSv vs 7-8-mSv). To reduce this risk further, newer programmes are now using ultra-low dose CTs, which can achieve a dose one-tenth of conventional LDCT[62]. Whilst exposure from a single LDCT is not concerning, repeated scanning over a participant's lifetime carries risk that needs to be justified in the

screening selection process, in addition to risks from downstream imaging of positive finding, such as Positron Emission Tomography (PET) CT and image guided biopsies. Nonetheless, several studies have defined the risk of radiation-induced cancer deaths as a consequence of LDCT lung cancer screening to be very low and not enough to outweigh the potential benefits[63-65].

Overdiagnosis is the finding of a cancer through screening that would have never caused harm within the patient's lifetime, either due to the indolent biology of the tumour or due to death from competing causes of mortality. In large RCTs, overdiagnosis is measured as the excess number of lung cancers in the intervention arm as compared with the control arm, with a large span of reported figures ranging from none in the ITALUNG study to 67% in DLCST[66,67]. In NLST, the overdiagnosis rate was initially estimated at 18%[18]. Weaknesses with this estimation included a short period of follow-up, only 6.5 years, not long enough to overcome lead-time bias, and included treatment of indolent bronchioloalveolar carcinomas (BAC), which accounted for almost 80% of the overdiagnosed cases, and entity now managed conservatively. Recent publication of updated NLST follow-up data after a longer period of 11 years suggests the overdiagnosis rate to be closer to 3%[68]. More recently, the NELSON trial estimated an overdiagnosis upper limit of 8.9%, expected to reduce further over time. The risk of overdiagnosis can potentially be reduced further by identifying and addressing other smoking-related competing caused of mortality, such as cardiovascular disease and COPD, and by incorporating a selection process by which those most likely to benefit, in terms of life-years gained, are identified for screening, though the evidence-base for this approach is still developing.

LDCT scans detect benign nodules as well as lung cancers, which provides a challenge for screening programmes. Investigation and treatment of a screen-detected benign lesion is deemed to be a false positive result and harms associated to this include stress and anxiety, though this tends to be short-lived[69], as well as physical complications as a consequence of invasive investigations and, ultimately, surgery. The definition of positive nodules has varied across screening trials, leading to a wide range of reported false positive rates (1.3%-28.8%). The use of detailed, evidence-based, pulmonary nodules

management algorithms[70,71] has been shown to reduce the rate of false positive findings. As an illustration, the reported false positive rate in NLST, where any non-calcified nodule ≥4mm was defined as positive, was 23.3%. In comparison, NELSON, where volumetric measurements, larger positive size definitions and surveillance groups identified, reported much lower false positive rates of 1.2%. More recently, real-world data from five UK-based screening programmes reported an overall false positive rate of 2.2%, significantly lower than that reported in NLST and the majority of European screening trials outside of NELSON[72].

Managing incidental findings during lung cancer screening

LDCT scans produce images from the lower neck to the upper abdomen and leads to the identification of significant numbers of incidental findings (IFs) in those areas[73]. IFs in lung cancer screening are defined as LDCT findings that can potentially affect the health of the patient and are not related to lung cancer itself[74]. The ever-increasing numbers of screening programmes internationally means that IFs are becoming increasingly prevalent internationally. The prevalence of IFs in screening populations is highly variable, particularly as there is no international consensus guidelines as to how they should be classified and managed. As a result, IF prevalence rates have ranged between 1%-41% across studies[75,76], although generally significantly lower number of patients have findings that require further intervention[77]. The American College of Radiology (ACR) Lung CT Screening Reporting and Data System (Lung-RADS) has an "S" modifier for clinically significant non-lung cancer findings with a reported prevalence rate of 10%, although the definition of these findings is arbitrary[78]. Many of these incidental findings are benign and clinically insignificant[79], but identification of others when coupled with appropriate interventions may also lead to a reduction in all-cause mortality as the targeted populations of lung cancer screening patients are also at risk for significant age and smoking related co-morbidities[80]. As such, effective screening programmes need to have strategies and resources in

place to effectively manage significant IFs in order to benefit the populations it serves and maintain safety.

The most common IFs occur in the cardiovascular system, followed by renal, pulmonary and hepatic lesions[81]. Up to 80% of patients undergoing CT thorax have and IF of coronary artery calcification. Although not as effective as specific Coronary CT examinations, LDCT scanning has been shown to correlate well with risk of death and therefore patients may benefit from intervention on severe disease incidentally found at screening[82]. Aortic Aneurysmal disease is another incidental cardiac finding found in over 8% of screening cases and aneurysmal dilatation of greater than 4.5cm should prompt specialist referral for surveillance imaging[77]. From a pulmonary perspective, the major IFs include emphysema, Interstitial Lung Disease (ILD), pulmonary infections and pleural abnormalities. Several studies have shown that LDCT can identify COPD with comparable accuracy to pulmonary function testing[83]. LDCT may identify COPD at an earlier stage than normally achieved through referral for spirometry and effective earlier interventions may be initiated, particularly smoking cessation, that may reduce the burden of disease. Similarly, earlier interventions may be initiated with the identification of ILD and pulmonary infections that may improve ling term outcomes. In Idiopathic Pulmonary Fibrosis particularly, early initiation of anti-fibrotic treatment such as Pirfenidone can result in overall mortality improvements[84]. Outside the cardiopulmonary systems, thyroid nodules, mediastinal masses, unexplained lymphadenopathy, non-pulmonary malignancies, renal and gallbladder calculi are identified occasionally and may require further intervention on a case by case basis[80].

Conclusions

Lung cancer remains a serious condition with poor outcomes and continues to be the world's biggest cause of cancer death. Diagnosis of symptomatic cancer is all too often delayed and more is needed in terms of public awareness campaigns, healthcare professional education and clinical pathways that increase presentation in primary care, increase CXR uptake and increase suspected lung cancer referrals for patients with persistent symptoms to improve the earlier diagnosis of symptomatic lung cancer. The evidence-base now exists to justify LDCT screening for asymptomatic high-risk populations, with three RCTs successfully demonstrating a mortality reduction, and recent real-life data from the UK has demonstrated that screening can be successfully implemented. However, to maximise benefits of screening on a wider scale, efforts must be made to optimise screening uptake, especially amongst high-risk populations with significant socioeconomic deprivation, integrate tobacco dependency treatment, minimise screening-related harms and adequately manage incidental findings in a quality assured and protocolised manner. By undertaking all of the above, there can be optimism that bleak trends in lung cancer outcomes can be improved upon significantly in the future.

Table 1: Details of selection, methods and results from European lung cancer screening RCTs

Study	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 (%)
DANTE	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	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	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	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	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	Single LDCT vs No Screen (Single round)	4,055	50-75	LLP_v2 ≥5%	1.7	85.7	83.0
NELSON	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

PY=Pack years; LDCT=Low-dose computer tomography; CPD=Cigarettes per day; LLP=Liverpool Lung Project risk model;$PLCO_{m2012}$=Prostate, Lung, Colorectal and Ovarian trial risk model, the 2012 model; PanCan=Pan-Canadian study risk model

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Lung Cancer Statistics. 2022. (Accessed 1st July, 2022, at http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/diagnosis-and-treatment)#heading-One.)
3. NLCA annual report 2022. 2022. (Accessed 1st July, 2022, at https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2022.)
4. NHS Long Term Plan. 2019. (Accessed 1st July, 2022, at https://www.longtermplan.nhs.uk/.)
5. Evison M, Taylor S, Grundy S, Perkins A, Peake M. Promoting early diagnosis and recovering from the COVID-19 pandemic in lung cancer through public awareness campaigns: learning from patient and public insight work. BMJ Open Respir Res 2021;8.
6. Lyratzopoulos G, Neal RD, Barbiere JM, Rubin GP, Abel GA. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. Lancet Oncol 2012;13:353-65.
7. Kennedy MPT, Cheyne L, Darby M, et al. Lung cancer stage-shift following a symptom awareness campaign. Thorax 2018;73:1128-36.
8. Bradley SH, Abraham S, Callister ME, et al. Sensitivity of chest X-ray for detecting lung cancer in people presenting with symptoms: a systematic review. Br J Gen Pract 2019;69:e827-e35.
9. Round T, Gildea C, Ashworth M, Moller H. Association between use of urgent suspected cancer referral and mortality and stage at diagnosis: a 5-year national cohort study. Br J Gen Pract 2020;70:e389-e98.
10. Frost JK, Ball WC, Jr., Levin ML, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. Am Rev Respir Dis 1984;130:549-54.
11. Fontana RS, Sanderson DR, Taylor WF, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. Am Rev Respir Dis 1984;130:561-5.
12. Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR. Lung cancer screening: the Mayo program. J Occup Med 1986;28:746-50.
13. Hocking WG, Hu P, Oken MM, et al. Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. J Natl Cancer Inst 2010;102:722-31.
14. Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA 2011;306:1865-73.
15. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99-105.
16. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early lung cancer action project: a summary of the findings on baseline screening. Oncologist 2001;6:147-52.
17. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996;201:798-802.
18. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
19. Humphrey LL, Deffebach M, Pappas M, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive services task force recommendation. Ann Intern Med 2013;159:411-20.
20. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 2020.
21. Pastorino U, Silva M, Sestini S, et al. Prolonged Lung Cancer Screening Reduced 10-year Mortality in the MILD Trial. Ann Oncol 2019.

22. Crosbie PA, Balata H, Evison M, et al. Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester. Thorax 2018.
23. Crosbie PA, Balata H, Evison M, et al. Second round results from the Manchester 'Lung Health Check' community-based targeted lung cancer screening pilot. Thorax 2019;74:700-4.
24. Ghimire B, Maroni R, Vulkan D, et al. Evaluation of a health service adopting proactive approach to reduce high risk of lung cancer: The Liverpool Healthy Lung Programme. Lung Cancer 2019;134:66-71.
25. Bartlett EC, Kemp SV, Ridge CA, et al. Baseline Results of the West London lung cancer screening pilot study - Impact of mobile scanners and dual risk model utilisation. Lung Cancer 2020;148:12-9.
26. Quaife SL, Ruparel M, Beeken RJ, et al. The Lung Screen Uptake Trial (LSUT): protocol for a randomised controlled demonstration lung cancer screening pilot testing a targeted invitation strategy for high risk and 'hard-to-reach' patients. BMC Cancer 2016;16:281.
27. Quaife SL, Ruparel M, Dickson JL, et al. Lung Screen Uptake Trial (LSUT): Randomized Controlled Clinical Trial Testing Targeted Invitation Materials. Am J Respir Crit Care Med 2020;201:965-75.
28. Narayan AK, Gupta Y, Little BP, Shepard JO, Flores EJ. Lung cancer screening eligibility and use with low-dose computed tomography: Results from the 2018 Behavioral Risk Factor Surveillance System cross-sectional survey. Cancer 2021;127:748-56.
29. Lopez-Olivo MA, Maki KG, Choi NJ, et al. Patient Adherence to Screening for Lung Cancer in the US: A Systematic Review and Meta-analysis. JAMA Netw Open 2020;3:e2025102.
30. McRonald FE, Yadegarfar G, Baldwin DR, et al. The UK Lung Screen (UKLS): demographic profile of first 88,897 approaches provides recommendations for population screening. Cancer Prev Res (Phila) 2014;7:362-71.
31. Hestbech MS, Siersma V, Dirksen A, Pedersen JH, Brodersen J. Participation bias in a randomised trial of screening for lung cancer. Lung Cancer 2011;73:325-31.
32. Pham D, Bhandari S, Pinkston C, Oechsli M, Kloecker G. Lung Cancer Screening Registry Reveals Low-dose CT Screening Remains Heavily Underutilized. Clin Lung Cancer 2020;21:e206-e11.
33. Rustagi AS, Byers AL, Keyhani S. Likelihood of Lung Cancer Screening by Poor Health Status and Race and Ethnicity in US Adults, 2017 to 2020. JAMA Netw Open 2022;5:e225318.
34. Robb KA. The integrated screening action model (I-SAM): A theory-based approach to inform intervention development. Prev Med Rep 2021;23:101427.
35. Quaife SL, Waller J, Dickson JL, et al. Psychological Targets for Lung Cancer Screening Uptake: A Prospective Longitudinal Cohort Study. J Thorac Oncol 2021;16:2016-28.
36. Quaife SL, Marlow LAV, McEwen A, Janes SM, Wardle J. Attitudes towards lung cancer screening in socioeconomically deprived and heavy smoking communities: informing screening communication. Health Expect 2017;20:563-73.
37. Smits SE, McCutchan GM, Hanson JA, Brain KE. Attitudes towards lung cancer screening in a population sample. Health Expect 2018;21:1150-8.
38. Carter-Harris L, Brandzel S, Wernli KJ, Roth JA, Buist DSM. A qualitative study exploring why individuals opt out of lung cancer screening. Fam Pract 2017;34:239-44.
39. Ali N, Lifford KJ, Carter B, et al. Barriers to uptake among high-risk individuals declining participation in lung cancer screening: a mixed methods analysis of the UK Lung Cancer Screening (UKLS) trial. BMJ Open 2015;5:e008254.
40. Duffy SW, Myles JP, Maroni R, Mohammad A. Rapid review of evaluation of interventions to improve participation in cancer screening services. J Med Screen 2017;24:127-45.
41. Rivera MP, Katki HA, Tanner NT, et al. Addressing Disparities in Lung Cancer Screening Eligibility and Healthcare Access. An Official American Thoracic Society Statement. Am J Respir Crit Care Med 2020;202:e95-e112.
42. Cadham CJ, Cao P, Jayasekera J, et al. Cost-Effectiveness of Smoking Cessation Interventions in the Lung Cancer Screening Setting: A Simulation Study. J Natl Cancer Inst 2021;113:1065-73.

43. Zeliadt SB, Heffner JL, Sayre G, et al. Attitudes and Perceptions About Smoking Cessation in the Context of Lung Cancer Screening. JAMA Intern Med 2015;175:1530-7.
44. Carter-Harris L, Ceppa DP, Hanna N, Rawl SM. Lung cancer screening: what do long-term smokers know and believe? Health Expect 2017;20:59-68.
45. Groves S, McCutchan G, Quaife SL, et al. Attitudes towards the integration of smoking cessation into lung cancer screening in the United Kingdom: A qualitative study of individuals eligible to attend. Health Expect 2022.
46. McBride CM, Ostroff JS. Teachable moments for promoting smoking cessation: the context of cancer care and survivorship. Cancer Control 2003;10:325-33.
47. Kathuria H, Koppelman E, Borrelli B, et al. Patient-Physician Discussions on Lung Cancer Screening: A Missed Teachable Moment to Promote Smoking Cessation. Nicotine Tob Res 2020;22:431-9.
48. Deppen SA, Grogan EL, Aldrich MC, Massion PP. Lung cancer screening and smoking cessation: a teachable moment? J Natl Cancer Inst 2014;106:dju122.
49. Balata H, Traverse-Healy L, Blandin-Knight S, et al. Attending community-based lung cancer screening influences smoking behaviour in deprived populations. Lung Cancer 2020;139:41-6.
50. Kummer S, Waller J, Ruparel M, Cass J, Janes SM, Quaife SL. Mapping the spectrum of psychological and behavioural responses to low-dose CT lung cancer screening offered within a Lung Health Check. Health Expect 2020;23:433-41.
51. Ashraf H, Saghir Z, Dirksen A, et al. Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: final results after a 5-year screening programme. Thorax 2014;69:574-9.
52. Brain K, Carter B, Lifford KJ, et al. Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial. Thorax 2017;72:912-8.
53. Clark MA, Gorelick JJ, Sicks JD, et al. The Relations Between False Positive and Negative Screens and Smoking Cessation and Relapse in the National Lung Screening Trial: Implications for Public Health. Nicotine Tob Res 2016;18:17-24.
54. Tammemagi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL. Impact of lung cancer screening results on smoking cessation. J Natl Cancer Inst 2014;106:dju084.
55. Iaccarino JM, Duran C, Slatore CG, Wiener RS, Kathuria H. Combining smoking cessation interventions with LDCT lung cancer screening: A systematic review. Prev Med 2019;121:24-32.
56. Murray RL, Brain K, Britton J, et al. Yorkshire Enhanced Stop Smoking (YESS) study: a protocol for a randomised controlled trial to evaluate the effect of adding a personalised smoking cessation intervention to a lung cancer screening programme. BMJ Open 2020;10:e037086.
57. Joseph AM, Rothman AJ, Almirall D, et al. Lung Cancer Screening and Smoking Cessation Clinical Trials. SCALE (Smoking Cessation within the Context of Lung Cancer Screening) Collaboration. Am J Respir Crit Care Med 2018;197:172-82.
58. Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. N Engl J Med 2013;368:351-64.
59. Ruparel M, Quaife SL, Dickson JL, et al. Evaluation of cardiovascular risk in a lung cancer screening cohort. Thorax 2019;74:1140-6.
60. Balata H, Blandin Knight S, Barber P, et al. Targeted lung cancer screening selects individuals at high risk of cardiovascular disease. Lung Cancer 2018;124:148-53.
61. Steiger D, Siddiqi MF, Yip R, Yankelevitz DF, Henschke CI, investigators IE. The importance of low-dose CT screening to identify emphysema in asymptomatic participants with and without a prior diagnosis of COPD. Clin Imaging 2021;78:136-41.
62. Huber A, Landau J, Ebner L, et al. Performance of ultralow-dose CT with iterative reconstruction in lung cancer screening: limiting radiation exposure to the equivalent of conventional chest X-ray imaging. Eur Radiol 2016;26:3643-52.
63. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 2012;307:2418-29.

64. Rintoul RC, Atherton R, Tweed K, Yates S, Chilvers ER. Exposure of patients to ionising radiation during lung cancer diagnostic work-up. Thorax 2017;72:853-5.
65. Rampinelli C, De Marco P, Origgi D, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. BMJ 2017;356:j347.
66. Heleno B, Siersma V, Brodersen J. Estimation of Overdiagnosis of Lung Cancer in Low-Dose Computed Tomography Screening: A Secondary Analysis of the Danish Lung Cancer Screening Trial. JAMA Intern Med 2018;178:1420-2.
67. Paci E, Puliti D, Lopes Pegna A, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax 2017.
68. Black WC, Chiles C, Church TR, et al. Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial National Lung Screening Trial Writing Team (1). J Thorac Oncol 2019.
69. van den Bergh KA, Essink-Bot ML, Borsboom GJ, Scholten ET, van Klaveren RJ, de Koning HJ. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. Eur Respir J 2011;38:154-61.
70. Manos D, Seely JM, Taylor J, Borgaonkar J, Roberts HC, Mayo JR. The Lung Reporting and Data System (LU-RADS): a proposal for computed tomography screening. Can Assoc Radiol J 2014;65:121-34.
71. Callister ME, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax 2015;70 Suppl 2:ii1-ii54.
72. Balata H, Ruparel M, O'Dowd E, et al. Analysis of the baseline performance of five UK lung cancer screening programmes. Lung Cancer 2021;161:136-40.
73. Kauczor H-U, Baird A-M, Blum TG, et al. ESR/ERS statement paper on lung cancer screening. European radiology 2020;30:3277-94.
74. Penha D, Pinto E, Monaghan C, et al. Incidental findings on lung cancer screening: pictorial essay and systematic checklist. Jornal Brasileiro de Pneumologia 2022;48.
75. Team NLSTR. Reduced lung-cancer mortality with low-dose computed tomographic screening. New England Journal of Medicine 2011;365:395-409.
76. Kinsinger LS, Anderson C, Kim J, et al. Implementation of lung cancer screening in the Veterans Health Administration. JAMA internal medicine 2017;177:399-406.
77. Morgan L, Choi H, Reid M, Khawaja A, Mazzone PJ. Frequency of incidental findings and subsequent evaluation in low-dose computed tomographic scans for lung cancer screening. Annals of the American Thoracic Society 2017;14:1450-6.
78. Ngoc TB, Lan NTP. LOW DOSE COMPUTER TOMOGRAPHY BY “LUNG-RADS” TOOL FOR SCREENING AND EARLY LUNG CANCER DETECTING.
79. Chung JH, Richards JC, Koelsch TL, MacMahon H, Lynch DA. Screening for lung cancer: incidental pulmonary parenchymal findings. American Journal of Roentgenology 2018;210:503-13.
80. Tsai EB, Chiles C, Carter BW, et al. Incidental findings on lung cancer screening: significance and management. Seminars in Ultrasound, CT and MRI; 2018: Elsevier. p. 273-81.
81. Reiter MJ, Nemesure A, Madu E, Reagan L, Plank A. Frequency and distribution of incidental findings deemed appropriate for S modifier designation on low-dose CT in a lung cancer screening program. Lung cancer (Amsterdam, Netherlands) 2018;120:1-6.
82. Pakdaman MN, Rozanski A, Berman DS. Incidental coronary calcifications on routine chest CT: Clinical implications. Trends in Cardiovascular Medicine 2017;27:475-80.
83. Mets OM, Schmidt M, Buckens CF, et al. Diagnosis of chronic obstructive pulmonary disease in lung cancer screening computed tomography scans: independent contribution of emphysema, air trapping and bronchial wall thickening. Respiratory research 2013;14:1-8.
84. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. American journal of respiratory and critical care medicine 2015;192:e3-e19.